PATENTTI- JA REKISTERIHALLITUS
NATIONAL BOARD OF PATENTS AND REGISTRATION

PCT/FI2004/000447

Helsinki 16.08.2004

REC'D 24 SEP 2004
WIPO PCT

E T U O I K E U S T O D I S T U S
P R I O R I T Y D O C U M E N T

Hakija
Applicant

1. Biotie Therapies Corporation, Turku, FI
2. Smith, David, Naantali, FI
3. Marjamäki, Anne, Littoinen, FI
4. Ojala, Marika, Raisio, FI
5. Pihlavisto, Marjo, Kaarina, FI
6. Heino, Jyrki, Turku, FI
7. Käpylä, Jarmo, Jyväskylä, FI
8. Pentikäinen, Olli, Lieto, FI
9. Nyrönen, Tommi, Helsinki, FI
10. Johnson, Mark, Turku, FI
11. Huhtala, Mikko, Turku, FI

Kansainvälinen patenttihakemus nro
International patent application no PCT/FI2004/000160

Kansainvälinen tekemispäivä
International filing date 19.03.2004

Keksinnön nimitys
Title of invention

"Sulphonamide derivatives"

Täten todistetaan, että oheiset asiakirjat ovat tarkkoja jäljennöksiä kansainvälisiä patenttihakemuksia vastaanottavana viranomaisena toimivalle Patentti- ja rekisterihallitukselle alkuaan annetuista selityksestä, patenttivaatimuksista, tiivistelmästä ja piirustuksista sekä niihin tehdyistä korjauksista.

This is to certify that the annexed documents are true copies of the description, claims, abstract and drawing, originally filed with the Finnish Patent Office acting as receiving Office for the international patent applications, and of any corrections thereto.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Marketta Tehikoski
Apulaistarkastaja

Maksu 50 €
Fee 50 Eur
Maksu perustuu kauppa- ja teollisuusministeriön antamaan asetukseen 1027/2001 Patentti- ja rekisterihallituksen maksullisista suoritteista muutoksineen.

The fee is based on the Decree with amendments of the Ministry of Trade and Industry No. 1027/2001 concerning the chargeable services of the National Board of Patents and Registration of Finland.

Osoite: Arkadiankatu 6 A
Address: P.O.Box 1160
FIN-00101 Helsinki, FINLAND
Puhelin: 09 6939 500
Telephone: + 358 9 6939 500
Telefax: 09 6939 5328
Telefax: + 358 9 6939 5328

HOME COPY

2022586PC

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	PCT/FI2004/000160
0-2	International Filing Date	19 MAR 2004 (19-03-2004)
0-3	Name of receiving Office and "PCT International Application"	The Finnish Patent Office PCT International Application
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.158)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	National Board of Patents and Registration (Finland) (RO/FI)
0-7	Applicant's or agent's file reference	2022586PC
I	Title of Invention	SULPHONAMIDE DERIVATIVES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	BIOTIE THERAPIES CORPORATION
II-5	Address:	Tykistökatu 6 FI-20520 Turku Finland
II-6	State of nationality	FI
II-7	State of residence	FI
III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	SMITH, David
III-1-5	Address:	Valliuksenkatu 6 FI-21100 Naantali Finland
III-1-6	State of nationality	GB
III-1-7	State of residence	FI

III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	MARJAMÄKI, Anne
III-2-5	Address:	Käpäläkuja 7 FI-20660 Littoinen Finland
III-2-6	State of nationality	FI
III-2-7	State of residence	FI
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	OJALA, Marika
III-3-5	Address:	Vainiontie 42 FI-21120 Raisio Finland
III-3-6	State of nationality	FI
III-3-7	State of residence	FI
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	PIHLAVISTO, Marjo
III-4-5	Address:	Kuminakatu 10 FI-20780 Kaarina Finland
III-4-6	State of nationality	FI
III-4-7	State of residence	FI
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	HEINO, Jyrki
III-5-5	Address:	Murkionkatu 26 FI-20740 Turku Finland
III-5-6	State of nationality	FI
III-5-7	State of residence	FI

PCT REQUEST

Original (for SUBMISSION)

III-6	**Applicant and/or Inventor**	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	KÄPYLÄ, Jarmo
III-6-5	Address:	Mastonkaari 14 FI-40460 Jyväskylä Finland
III-6-6	State of nationality	FI
III-6-7	State of residence	FI
III-7	**Applicant and/or inventor**	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	PENTIKÄINEN, Olli
III-7-5	Address:	Puutarhankatu 23 as 6 FI-20100 Turku Finland
III-7-6	State of nationality	FI
III-7-7	State of residence	FI
III-8	**Applicant and/or inventor**	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	NYRÖNEN, Tommi
III-8-5	Address:	Eerikinkatu 25 C 61 FI-00180 Espoo Finland
III-8-6	State of nationality	FI
III-8-7	State of residence	FI
III-9	**Applicant and/or inventor**	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	JOHNSON, Mark
III-9-5	Address:	Arvinkatu 6 B 1-2 FI-20100 Turku Finland
III-9-6	State of nationality	GB
III-9-7	State of residence	FI

2022586PC

PCT REQUEST

Original (for SUBMISSION.)

III-10	**Applicant and/or inventor**	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	HUHTALA, Mikko
III-10-5	Address:	Rakuunatie 59 E 44 FI-20720 Turku Finland
III-10-6	State of nationality	FI
III-10-7	State of residence	FI
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name:	KOLSTER OY AB
IV-1-2	Address:	Iso Roobertinkatu 23 P.O. Box 148 FI-00121 Helsinki Finland
IV-1-3	Telephone No.	+ 358 9 618 821
IV-1-4	Facsimile No.	+ 358 9 602 244
IV-1-5	e-mail	kolster@kolster.fi
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the International filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	20 March 2003 (20.03.2003)
VI-1-2	Number	20030415
VI-1-3	Country	FI
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	**International Searching Authority Chosen**	Swedish Patent Office (ISA/SE)

2022586PC

PCT REQUEST

Original (for **SUBMISSION**)

VII-2	**Request to use results of earlier search; reference to that search**		
VII-2-1	Date	23 September 2003 (23.09.2003)	
VII-2-2	Number	20030415	
VII-2-3	Country (or regional Office)	FI	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	51	-
IX-3	Claims	3	-
IX-4	Abstract	2	✓
IX-5	Drawings	2	-
IX-7	TOTAL	64	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other:	Copy of official action	
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name:	KOLSTER OY AB	
X-1-2	Name of signatory	by Tapio Valkeiskangas	
X-1-3	Capacity		

2022586PC

PCT REQUEST

Original (for **SUBMISSION**)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	19 MAR 2004 (19-03-2004)
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/SE
10-6	Transmittal of search copy delayed until search fee is paid	

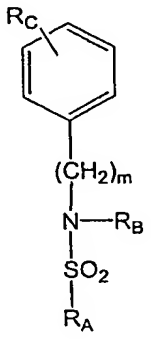
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

Sulphonamide derivatives

Field of the invention

The present invention relates to sulphonamide derivatives of formula (I),



(I)

where

R_C is an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or

R_C is $-NR^1R^2$, where

R^1 is hydrogen or alkyl,

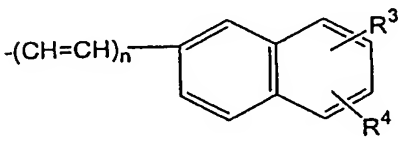
R^2 is alkyl or an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or

R^1 and R^2 taken together with the nitrogen atom to which they are attached form a heterocyclic group, which may contain one or more additional heteroatoms selected from O and N and which may be substituted, or

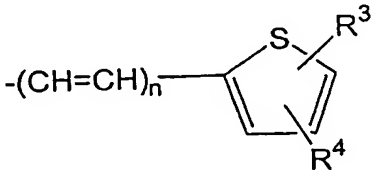
R^1 and R^2 are absent and the nitrogen atom together with the adjacent carbon atom forms a heterocyclic ring, which may contain one or more additional heteroatoms selected from N and S and which may be substituted,

m is 0 or 1,

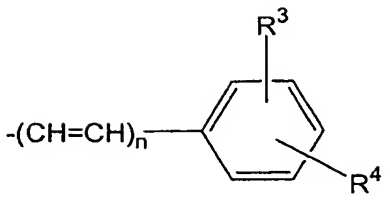
R_A is a group having the formula



(A),



(B) or



(C)

wherein

n is 0 or 1, and

R^3 and R^4 represent each independently hydrogen, halogen, aryl, alkoxy, carboxy, hydroxy, alkoxyalkyl, alkoxycarbonyl, cyano, trifluoromethyl, alkanoylamino, trifluoromethoxy, an optionally substituted aryl or heterocyclic group, and

R_B is hydrogen or alkyl.

The invention also relates to the use of the derivatives of formula (I) as inhibitors of collagen receptor integrins, especially $\alpha 2\beta 1$ integrin inhibitors and more precisely $\alpha 2\beta 1$ integrin I-domain inhibitors, e.g. in connection with diseases and medical conditions that involve the action of cells and platelets expressing collagen receptors, their use as a medicament, e.g. for the treatment of thrombosis and cancer spread, pharmaceutical compositions containing them and a process for preparing them.

Background of the invention

The integrins are a large family of cell surface receptors, which mediate cell adhesion to extracellular matrix. They are composed of one α and one β subunit that form a noncovalently bound dimer. In man there are eight β and eighteen α subunits that can form 24 different combinations. Integrins can be divided into three subcategories, namely (i) fibronectin and vitronectin receptors, which recognize an RGD-motif in their ligands, (ii) laminin receptors, and (iii) integrins that have a special inserted-domain (I-domain) in their α subunit. The I-domain integrins have been found only in Chordates (includes vertebrates), but not in Nematodes or Arthropods (Hynes *et al., J. Cell Biol., 2000, 150*:F89-96). Four out of nine I-domain integrins, namely $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$ and $\alpha 11\beta 1$ are collagen receptors (Gullberg *et al., Prog Histochem Cytochem., 2002, 37*:3-54). Collagens are the most abundant extracellular matrix proteins. Twenty-six collagen subtypes (types I-XXVI) are known at the moment (Myllyharju and Kivirikko, 2001, *Ann. Med. 33*:7-21). In man all four collagen receptor integrins have different expression pattern. Integrin $\alpha 2\beta 1$ is expressed on epithelial cells, platelets, endothelial cells, fibroblasts, chondrocytes (Zutter and

Santoro, *Am. J. Pathol., 1990, 137*:113-120), lymphocytes, mast cells (Kruger-Krasagakes *et al., J. Invest. Dermatol., 1996, 106*:538-543), and neutrophilic granulocytes (Werr *et al., Blood, 2000, 95*:1804-1809). Integrin $\alpha 2\beta 1$ deficient knock-out animals are viable, but their platelets do not react to stimulation with collagen (Chen *et al., Am. J. Pathol., 2002, 161*:337-344; Holtkotter *et al., J. Biol. Chem., 2002, 277*:10789-10794). In animal models $\alpha 2\beta 1$ also seems to participate in cancer-related angiogenesis (Senger *et al., Proc. Natl. Acad. Sci. U.S.A., 1997, 94*:13612-13617; Senger *et al., Am. J. Pathol., 2002, 160*:195-204) and chronic inflammation (de Fougerolles *et al., J. Clin. Invest., 2000, 105*:721-729). Epidemiological studies have indicated that in man high level of $\alpha 2\beta 1$ integrin on platelet surface is a risk factor for cerebrovascular stroke and myocardial infarction (Moshfegh *et al., Lancet, 1999, 353*:351-354; Carlsson *et al., Blood, 1999, 93*:3583-3586). In addition, integrin $\alpha 2\beta 1$ is expressed on variable cancer cell types, and is involved with invasion and progression of melanoma (Klein *et al., J. Invest. Dermatol., 1991, 96*:281-284), ovarian cancer (Fishman *et al., Invasion Metastasis, 1998,18*:15-26), prostate cancer (Bonkhoff *et al., Hum. Pathol., 1993, 24*:243-248), and gastric cancer (Kawamura *et al., Int. J. Oncol., 2001, 18*:809-815).

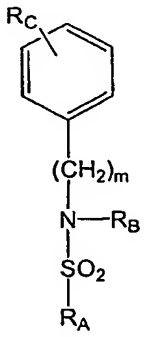
The collagen receptor integrins use their αI-domains in ligand recognition and binding. Human recombinant αI-domains have been used to analyze to molecular details of the binding mechanism (Emsley *et al., Cell, 2000, 101*:47-56). In all four collagen binding αI-domains (termed as α1I, α2I, α10I, α11I) the basic structure is very similar. However, αI-domain binding assays have indicated that their ligand binding mechanisms and, for example, their ability to bind to different collagen subtypes is different (Gullberg *et al., Prog Histochem Cytochem., 2002, 37*:3-54).

One known inhibitor of α2I-domain binding is a cyclic compound disclosed in the international patent publication WO 9902551.

It has now surprisingly been found that the compounds of formula (I) according to the present invention are potent inhibitors for collagen receptor integrins, especially $\alpha 2\beta 1$ integrin, and may be used in the treatment of human diseases, such as thrombosis, cancer, fibrosis and inflammation. The compounds of formula (I) may also be used in diagnostic methods both *in vitro* and *in vivo*.

Summary of the invention

The present invention relates sulphonamide derivatives of formula (I),



(I)

where

R_C is an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or R_C is $-NR^1$, NR^2, where

R^1 is hydrogen or alkyl,

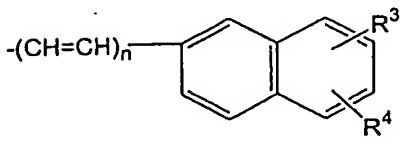
R^2 is alkyl or an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or

R^1 and R^2 taken together with the nitrogen atom to which they are attached form a heterocyclic group, which may contain one or more additional heteroatoms selected from O and N and which may be substituted, or

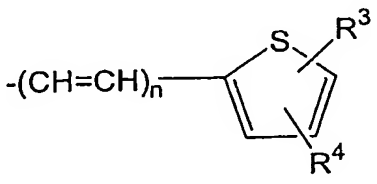
R^1 and R^2 are absent and the nitrogen atom together with the adjacent carbon atom forms a heterocyclic ring, which may contain one or more additional heteroatoms selected from N atoms or one S atom and which may be substituted,

m is 0 or 1,

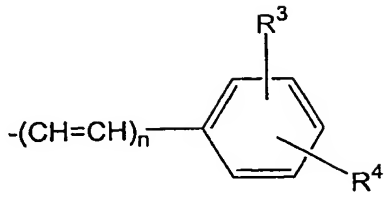
R_A is a group having the formula



(A),



(B) or



(C)

wherein

n is 0 or 1, and

R^3 and R^4 represent each independently hydrogen, halogen, aryl, alkoxy, carboxy, hydroxy, alkoxyalkyl, alkoxycarbonyl, cyano, trifluoromethyl, alkanoylamino, trifluoromethoxy, an optionally substituted aryl or heterocyclic group.

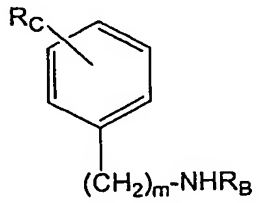
Further the invention relates to derivatives of formula (I) for use as inhibitors for collagen receptor integrins specifically $\alpha 2\beta 1$ integrin inhibitors and more precisely $\alpha 2\beta 1$ integrin I-domain inhibitors.

The invention also relates to derivatives of formula (I) for use as a medicament.

Further the invention relates to the use of a derivative of formula (I) for preparing a pharmaceutical composition for treating disorders relating to thrombosis and cancer spread.

The present invention also relates to a pharmaceutical composition comprising an effective amount of a derivative of formula (I) in admixture with a pharmaceutically acceptable carrier.

Further the invention relates to a process for preparing benzenesulphonamide derivatives of formula (I) comprising reacting a compound of formula (II),



(II)

where R_B, R_C and m are as defined above, with a compound of formula (III),

$$R_A\text{-}SO_2hal \qquad (III)$$

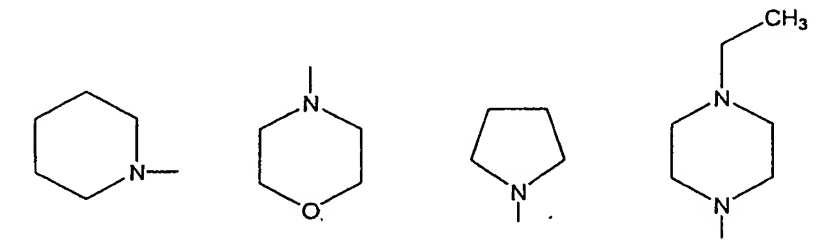
where R_A is as defined above and hal is halogen.

Detailed description of the invention

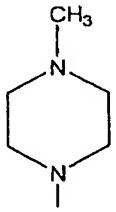
In the definition of the compound group of formula (I), the term "alkyl" refers to branched or straight chain alkyl groups having suitably 1 to 6 carbon atoms, preferably 1 to 3 carbon atoms, specifically methyl.

Examples of the meaning "4-6-membered heterocyclic ring containing at least one N atom" for R^2 are pyridyl and pyrimidinyl.

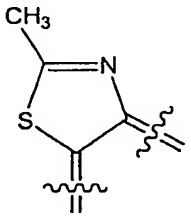
Typical examples of heterocyclic groups formed by R^1 and R^2 together with the N atom to which they are attached are groups having formulae



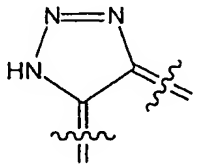
and



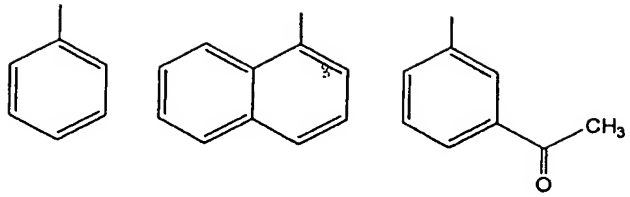
When R^1 and R^2 are absent the N atom may form together with the adjacent carbon atom in the phenyl ring a fused ring e.g. of formula



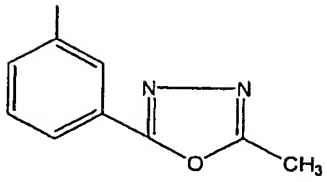
and



In formulae (A), (B) and (C) the meaning of "n" is preferably 0. Typical examples of R^3 and R^4 having the meaning alkoxyalkyl, alkoxycarbonyl and alkanoyl are those containing 1 to 6 carbon atoms in the alkoxy moiety and 1 to 6 carbon atoms in the alkyl moiety. Examples of optionally substituted aryl and heterocyclic groups are



and



Specific examples of preferred compounds are

3',4'dimetoxy-biphenyl-3-sulphonic acid (4-dimethylamino-phenyl)-amide),

N-[4-(dimethylamino)phenyl]-4'-fluoro-1',1'-biphenyl-3-sulphon-amide,

2,4-dichloro-N-{4-[(4,6-dimethylpyrimidin-2-yl)(methyl)amino]phen-yl}benzenesulphonamide,

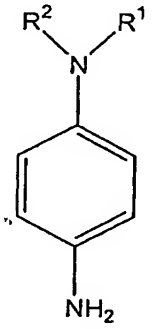
N-[4-(dimethylamino)phenyl]-3-(5-methyl-1,3,4-oxadiazol-2-yl)ben-zenesulphonamide,

2,4-dichloro-N-[4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]benzenesulphonamide,

2,4-dichloro-N-(2-methyl-1,3-benzothiazoll-5-yl)]benzenesulphon-amide,

N-[4-(dimethylamino)phenyl]-4-(1-naphtyl)benzenesulphonamide.

The compounds of formula (I) may be prepared by reacting a compound of formula (II)



(II)

where R_B, R_C and m are as defined above, with a compound of formula (III)

$$R_A\text{-}SO_2hal \qquad (III)$$

where R_A is as defined above and hal is halogen.

The reaction may be carried out in conventional manner using methods well-known to the person skilled in the art.

The pharmaceutical compositions can contain one or more of the sulphonamides of the invention. The administration can be parenteral, subcutaneous, intravenous, intraarticular, intrathecal, intramuscular, intraperitoneal or intradermal injections, or by transdermal, buccal, oromucosal, ocular routes or via inhalation. Alternatively or concurrently, administration can be by the oral route. The required dosage will depend upon the severity of the condition of the patient, for example, and such criteria as the patient's weight, sex, age, and medical history. The dose can also vary depending upon whether it is to be administered in a veterinary setting to an animal or to a human patient.

For the purposes of parenteral administration, compositions containing the sulphonamides of the invention are preferably dissolved in distilled water for injection and the pH preferably adjusted to about 6 to 8 and the solution is preferably adjusted to be isotonic. If the sulphonamide is to be provided in a lyophilized form, lactose or mannitol can be added to the solution as a bulking agent and, if necessary, buffers, salts, cryoprotectants and stabilizers can also be added to the composition to facilitate the lyophilization process, the solution is then filtered, introduced into vials and lyophilized.

Useful excipients for the compositions of the invention for parenteral administration also include sterile aqueous and non-aqueous solvents. The compounds of the invention may also be administered parenterally by using suspensions and emulsions as pharmaceutical forms. Examples of useful non-aqueous solvents include propylene glycol, polyethylene glycol, vegetable oil, fish oil, and injectable organic esters. Examples of aqueous carriers include water, water-alcohol solutions, emulsions or suspensions, including saline and buffered medical parenteral vehicles including sodium chloride solution, Ringer's dextrose solution, dextrose plus sodium chloride solution, Ringer's solution containing lactose, or fixed oils. Examples of intravenous infusion vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based upon Ringer's dextrose and the like.

Injectable preparations, such as solutions, suspensions or emulsions, may be formulated according to known art, using suitable dispersing or wetting agents and suspending agents, as needed. When the active compounds are in water-soluble form, for example, in the form of water soluble salts, the sterile injectable preparation may employ a non-toxic parenterally ac-

ceptable diluent or solvent as, for example, water for injection (USP). Among the other acceptable vehicles and solvents that may be employed are 5% dextrose solution, Ringer's solution and isotonic sodium chloride solution (as described in the Ph. Eur. / USP). When the active compounds are in a non-water soluble form, sterile, appropriate lipophilic solvents or vehicles, such as fatty oil, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides, are used. Alternatively, aqueous injection suspensions which contain substances which increase the viscosity, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran, and optionally also contain stabilizers may be used.

Pharmaceutical preparations for oral (but systemic) administration can be obtained by combining the active compounds with solid excipients, optionally granulating a resulting mixture and processing the mixture or granules or solid mixture without granulating, after adding suitable auxiliaries, if desired or necessary, to give tablets or capsules after filling into hard capsules.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose and/or starch preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as starches and their derivatives, pastes, using, for example, maize starch, wheat starch, rice starch, or potato starch, gelatine, tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and/or polyvinyl pyrrolidone, derivatives, and/or, if desired, disintegrating agents, such as the above-mentioned starches, and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, with suitable coating, which if desired, are resistant to gastric juices and for this purpose, *inter alia* concentrated sugar solutions, which optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures, but also film coating using cellulose derivatives, polyethylene glycols and/or PVP derivatives may be used. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate, are used for coating. Dyestuffs or pigments may be added to the tablets or dragee coatings, for example, for

identification or in order to characterize different combinations of active compound doses.

Solid dosage forms for oral administration include capsules, tablets, pills, troches, lozenges, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, pharmaceutical adjuvant substances, e.g., stearate lubricating agents or flavouring agents. Solid oral preparations can also be prepared with enteric or other coatings which modulate release of the active ingredients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert non-toxic diluents commonly used in the art, such as water and alcohol. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying, suspending, sweetening and flavouring agents.

The compositions of the invention may also be administered by means of pumps, or in sustained-release form. The compounds of the invention may also be delivered to specific organs in high concentration by means of suitably inserted catheters, or by providing such molecules as a part of a chimeric molecule (or complex) which is designed to target specific organs.

Administration in a sustained-release form is more convenient for the patient when repeated injections for prolonged periods of time are indicated so as to maximize the comfort of the patient. Controlled release preparation can be achieved by the use of polymers to complex or adsorb the peptides of the invention. Controlled delivery can be achieved by selecting appropriate macromolecules (for example, polyesters, polyamino acids, polyvinyl pyrrolidone, ethylenevinylacetate, methylcellulose, carboxymethylcelluloase protamine zinc and protamine sulfate) as well as the method of incorporation in order to control release. Another possible method to control the duration of action by controlled release preparations is to incorporate the desired peptide into particles of a polymeric material such as polyesters, polyamino acids, hydrogels, poly (lactic acid) or ethylene vinylacetate copolymers. Alternatively, instead of incorporating the sulphonamide into these polymeric particles, the sulphonamide can be entrapped into microparticles, prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly (methylmethacrylate) microcapsules, respectively, or in colloidal drug delivery systems, for example

liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules or in macroemulsions. The above-mentioned technics may be applied to both parenteral and oral administration of the pharmaceutical formulation.

The sulphonamides that are used in the compositions and methods of the invention can be employed in dosage forms such as tablets, coated tablets, capsules, powder sachets, or liquid solutions for oral administration if the biological activity of the material is not destroyed by the digestive process and if the characteristics of the compound allow it to be absorbed across the intestinal tissue.

The pharmaceutical compositions of the present invention can be manufactured in a manner which is in itself know, for example, by means of conventional mixing, granulating, dragee-making, dissolving, lyophilizing or similar processes.

The compounds of the invention are potent collagen receptor inhibitors and useful for inhibiting or preventing the adhesion of cells on collagen or the migration and invasion of cells through collagen, *in vivo* or *in vitro*. The now described compounds inhibit the migration of malignant cells and are thus for treating diseases such as cancers, including prostate, and melanoma, especially where $\alpha 2\beta 1$ integrin dependent cell adhesion/invasion/migration may contribute to the malignant mechanism.

The compounds of the invention also inhibit adhesion of platelets to collagen and collagen-induced platelet aggregation. Thus, the compounds of the invention are useful for treating patients in need of preventative or ameliorative treatment for conditions or diseases such as cardio-vascular diseases that are characterized by a need to prevent adhesion of platelets to collagen and collagen-induced platelet aggregation, for example, in stroke victims or patients at risk of having a stroke.

Pharmacological tests

A cell invasion assay was used to demonstrate the anti-cancer potential of the inhibitors *in vitro*

The ability to interact with extracellular matrix basement membranes is essential for the malignant cancer cell phenotype and cancer spread. $\alpha 2\beta 1$ levels are known to be upregulated in tumorigenic cells. The overexpression regulates cell adhesion and migration to and invasion through the extracellular

matrix. By blocking the interaction between extracellular matrix components like collagen and $\alpha 2\beta 1$ it is possible to block cancer cell migration and invasion *in vitro*. Prostate cancer cells (PC-3) expressing $\alpha 2\beta 1$ endogenously were used to test the *in vitro* anticancer potential of the inhibitors of the present invention.

Experimental procedure

Invasion of PC-3 cells (CRL-1435, ATCC) through Matrigel was studied using BD Biocoat invasion inserts (BD Biosciences). Inserts were stored at -20°C. Before the experiments inserts were allowed to adjust to the room temperature. 500 µl of serum free media (Ham's F12K medium, 2 mM L-glutamine, 1.5 g/l sodium bicarbonate) was added into the inserts and allowed to rehydrate at 37°C in cell incubator for two hours. The remaining media was aspirated. PC-3 cells were detached, pelleted and suspended into serum free media (50 000 cells / 500 µl). 300 µl of cell suspension was added into the insert in the absence (control) or presence of the inhibitor according to the present invention. Inserts were placed on the 24-well plates; each well containing 700 µl of cell culture media with 3% of fetal bovine serum as chemo-attractant. Cells were allowed to invade for 72 hours at 37°C in cell incubator. Inserts were washed with 700 µl PBS, and fixed with 4 % paraformaldehyde for 10 minutes. Paraformaldehyde was aspirated and cells were washed with 700 µl of PBS and inserts were stained by incubation with hematoxylin for 1 minute. The stain was removed by washing the inserts with 700 µl of PBS. Inserts were allowed to dry. Fixed invaded cells were calculated under the microscope. Invasion % was calculated as a comparison to the control. The results are presented in attached Figure 1.

A platelet function analyzer PFA100 was used to demonstrate the antithrombotic potential of the $\alpha 2\beta 1$ inhibitors

A platelet function analyzer PFA 100 was used to demonstrate the possible antithrombotic effects of $\alpha 2\beta 1$ inhibitors. The PFA 100 is a high shear-inducing device that simulates primary hemostasis after injury of a small vessel. The system comprises a test-cartridge containing a biologically active membrane coated with collagen plus ADP. An anticoaculated whole blood sample was run through a capillary under a constant vacuum. The platelet agonist (ADP) on the membrane and the high shear rate resulted in activation of platelet aggregation, leading to occlusion of the aperture with a stable plate-

let plug. The time required to obtain full occlusion of the aperture was designated as the "closure time". Each hit compound was added to the whole blood sample and the closure time was measured with PFA 100. If the closure time was increased when compared to the control sample the hit compound was suggested to have antithrombotic activity.

Experimental procedure

Blood was collected from a single donor via venipuncture into evacuated blood collection tubes containing lithium heparin as anticoagulant. Within 30 minutes, blood was aliquoted into 50 mL falcon tubes and treated with either inhibitory compounds (e.g. mAbs P1H5, *5E8,* P1E6) or, as controls, non-specific rat IgG or PBS only at pH 7.4. All experimental and control compounds were diluted in PBS before addition to 0.5% total volume (i.e. 15.92 mL blood and 80 μl compound in PBS). Samples were kept at room temperature with rotation for the duration of the experiments. Duplicate sample volumes (800 μl) were dispensed into PFA Collagen/ADP cartridges, and individual closure times were determined.

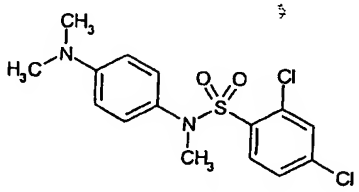
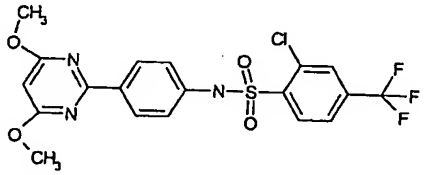
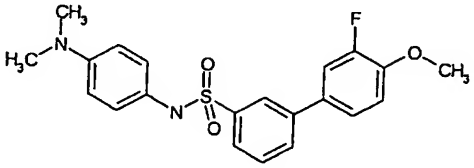
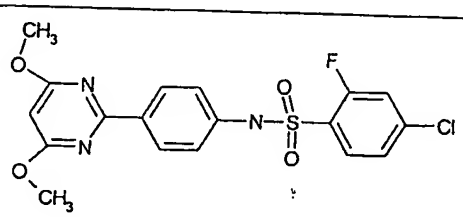
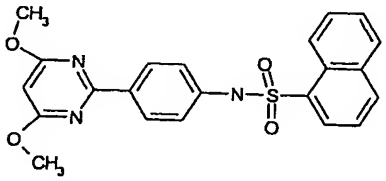
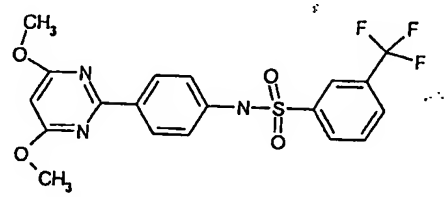
Control and experimental samples were tested in two or three sequences during the interval of 60 to 180 minutes from draw. This practice allowed the observation of increasing inhibitory effects over time.

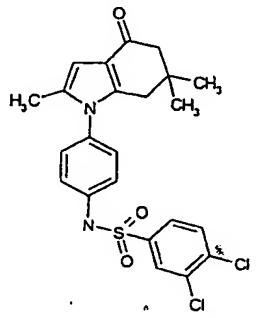
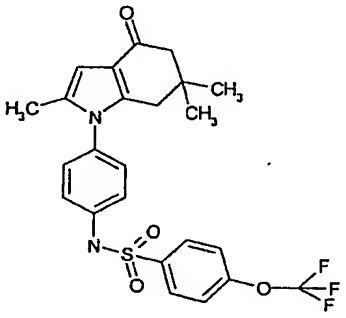
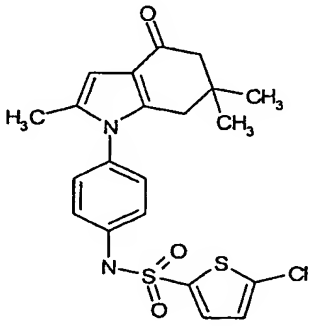
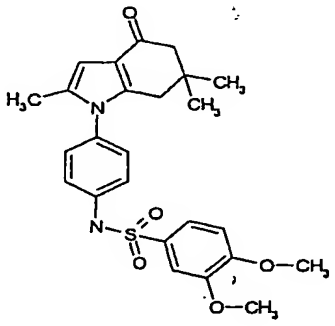
Acquisitions resulting in a closure time exceeding the range of measurement of the instrument (>300 seconds) were assigned a value of 300 seconds. Mean and standard deviations were calculated for each treatment, and data points falling outside ±2 SD of the mean were excluded. Student's t-test was applied to the resultant data. The results are presented in attached Figure 2.

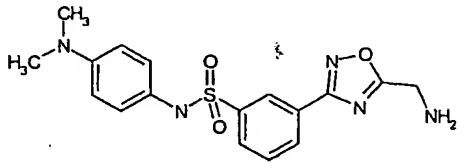
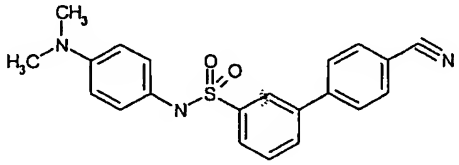
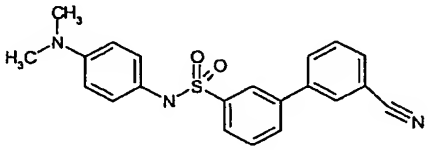
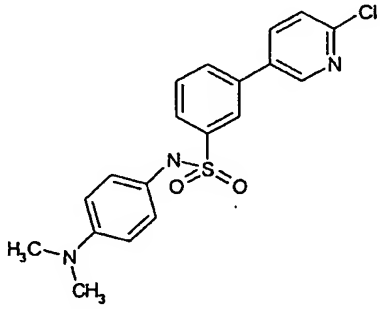
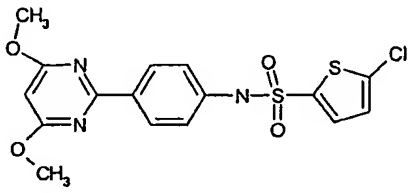
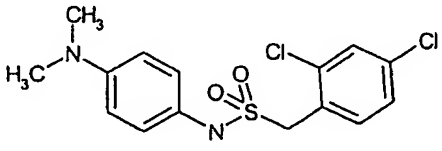
Figures 1 and 2 contain results with coded compounds BTT-3001 = 2,4-dichloro-N-{4-[(4,6-dimethylpyrimidin-2-yl)(methyl)amino]phenyl}benzene-sulphonamide, compound BTT-3002 = 3',4'-dimethoxy-biphenyl-3-sulphonic acid (4-dimethylamino-phenyl)-amide and compound BTT-3003 = N-[4-(dimethylamino)phenyl]-4'-fluoro-1',1'-biphenyl-3-sulphonamide.

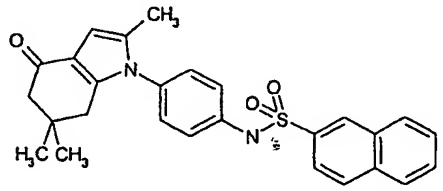
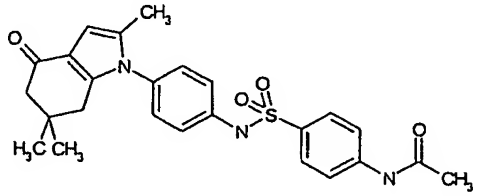
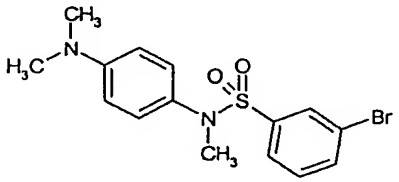
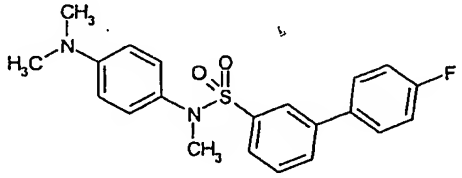
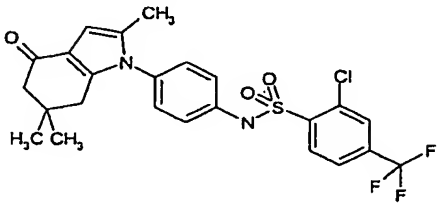
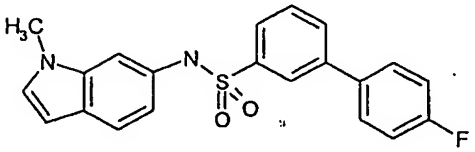
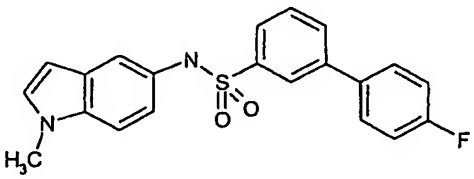
Further, the compounds listed in Table 1 and Table 1B below were tested. The results are presented in Table 2.

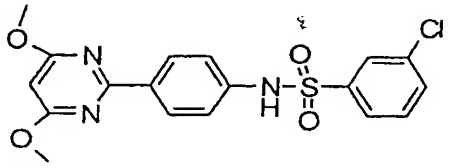
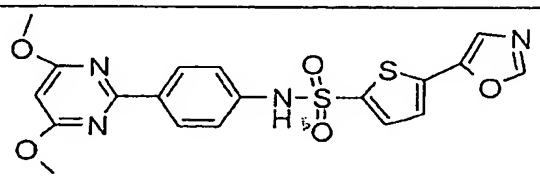
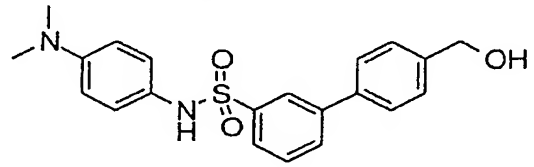
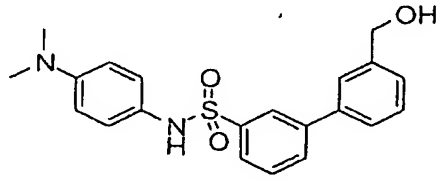
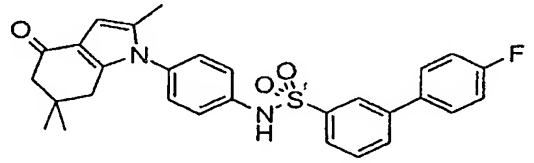
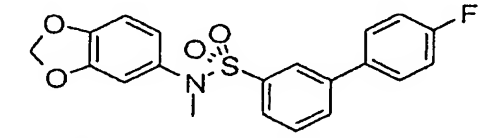
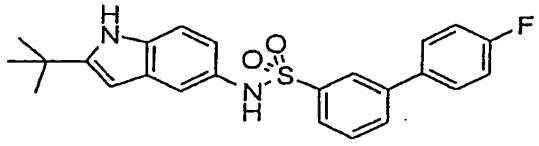
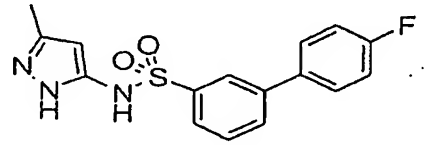
Table 1

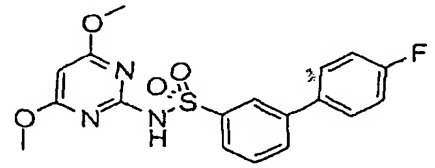
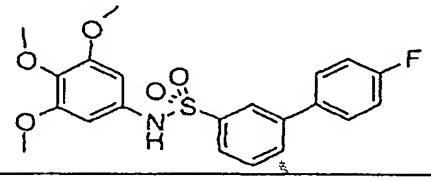
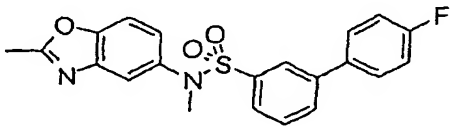
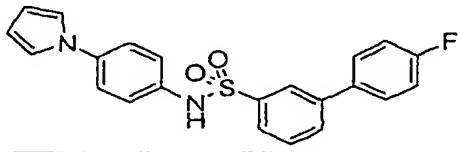
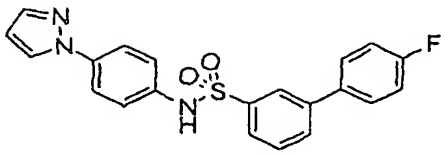
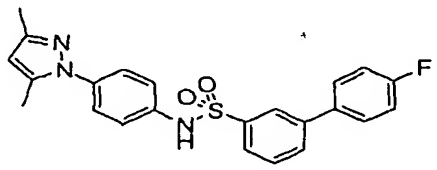
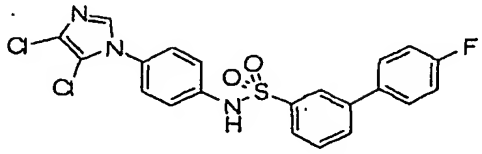
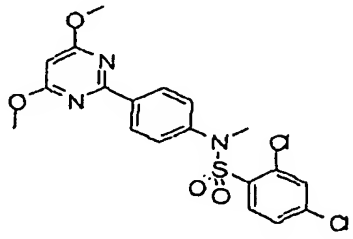
Structure	NCE number
	223
	256
	261
	265
	266
	268

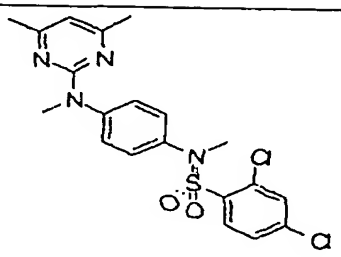
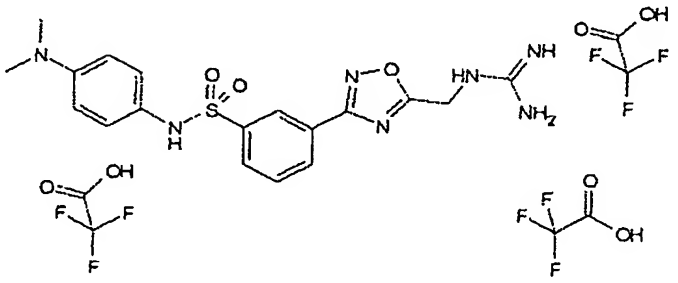
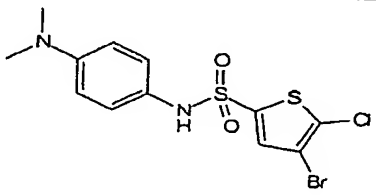
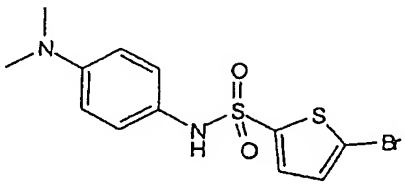
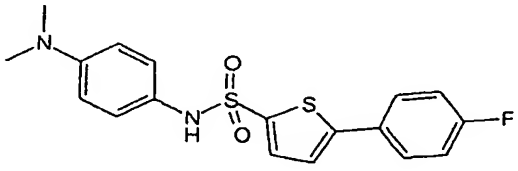
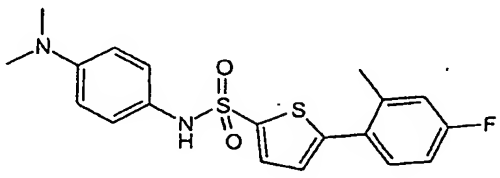
	269
	270
	271
	272

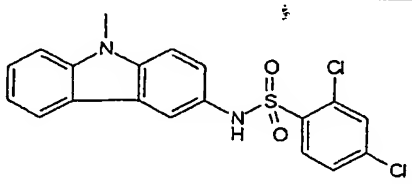
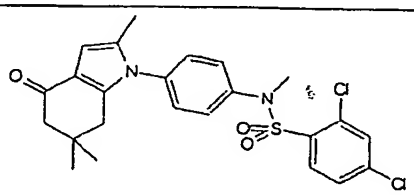
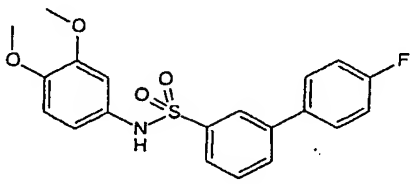
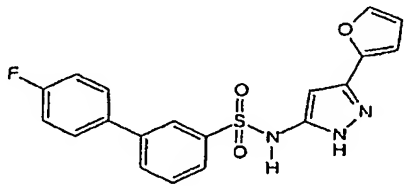
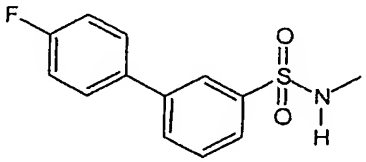
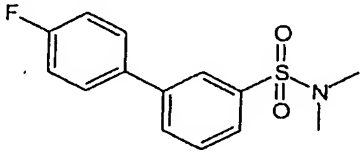
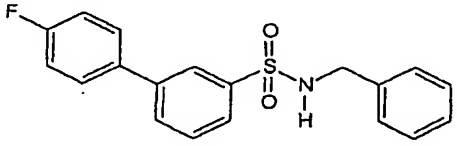
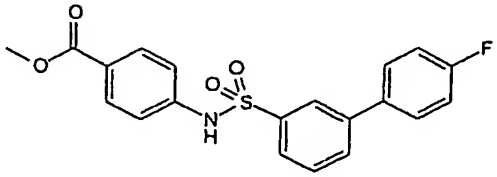
	273
	274
	275
	276
	277
	278

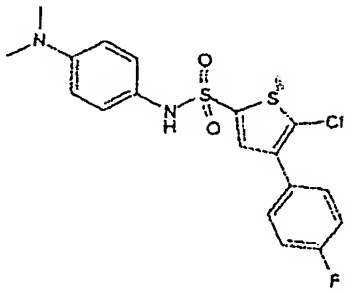
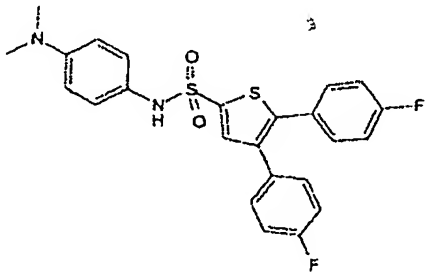
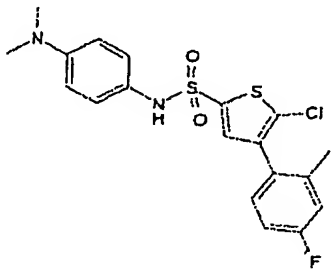
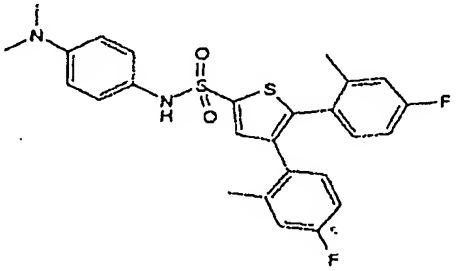
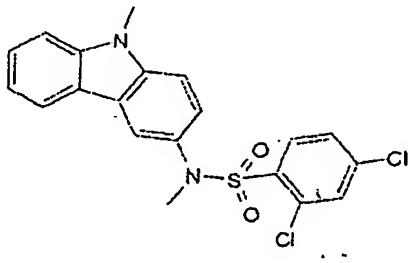
	279
	280
	281
	282
	283
	284
	285

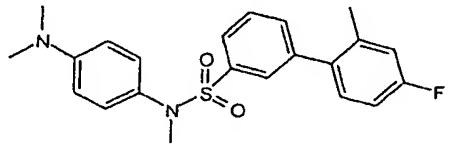
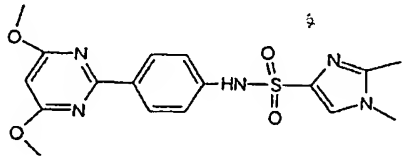
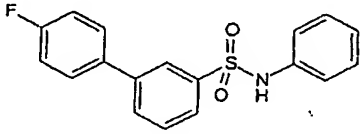
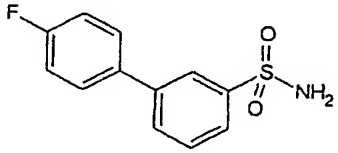
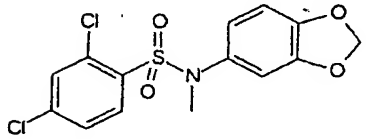
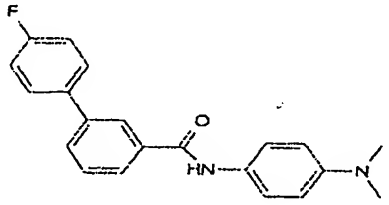
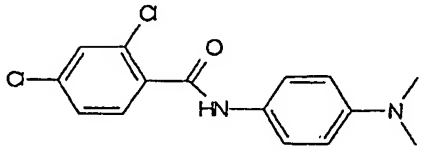
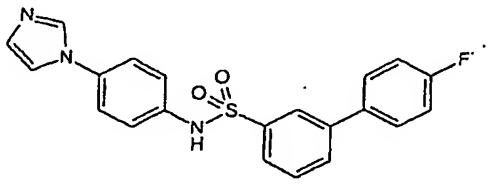
	267
	286
	287
	288
	289
	290
	291
	292

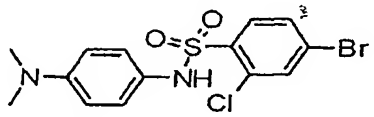
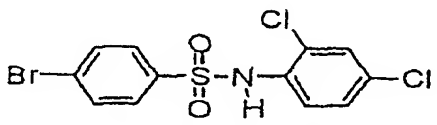
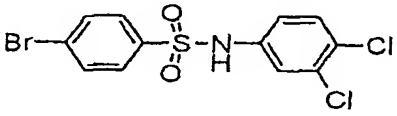
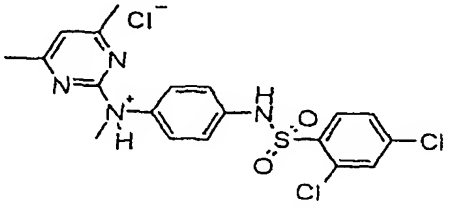
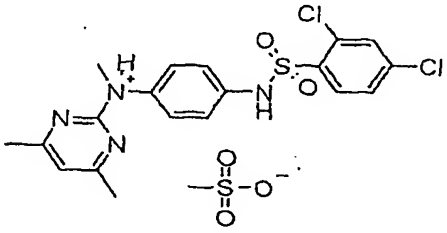
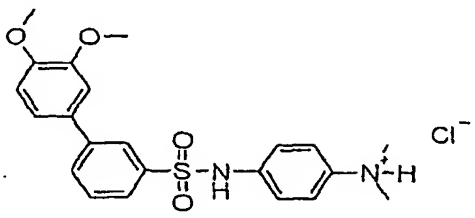
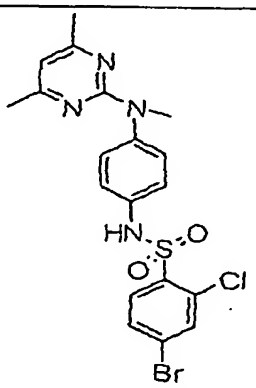
	293
	294
	295
	296
	297
	298
	299
	301

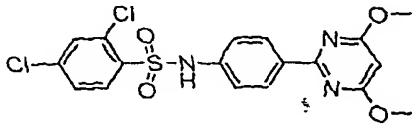
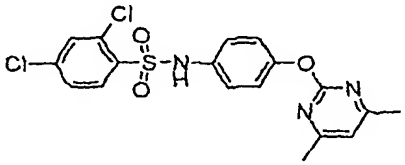
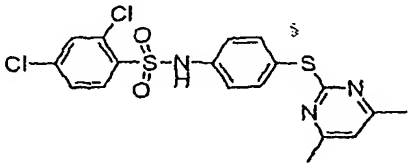
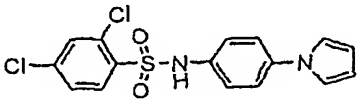
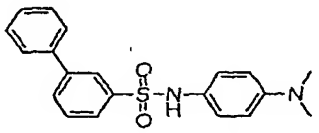
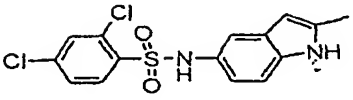
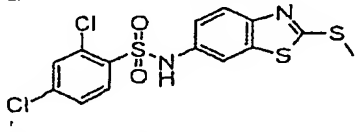
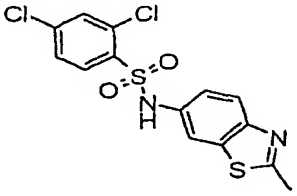
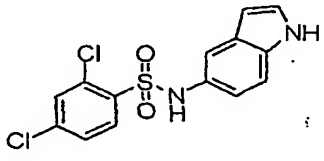
	302
	303
	304
	305
	306
	307

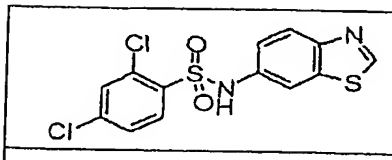
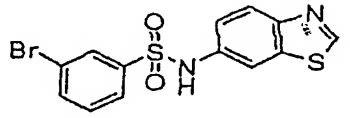
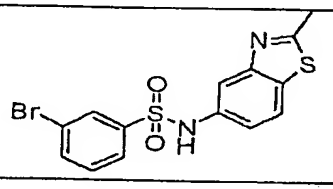
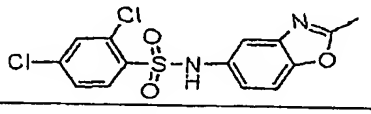
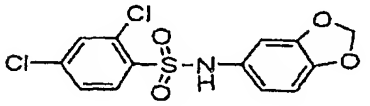
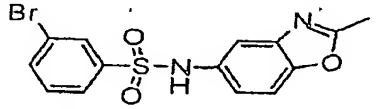
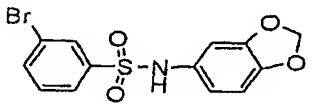
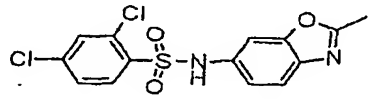
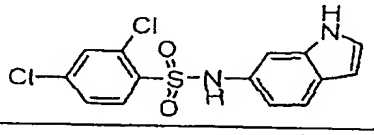
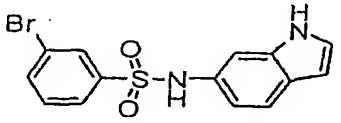
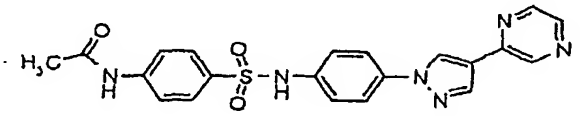
	308
	309
	310
	311
	312
	313
	314
	315

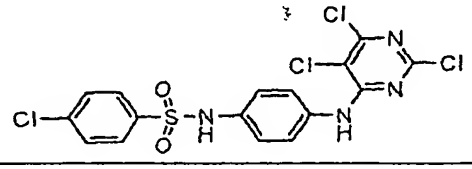
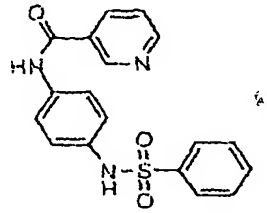
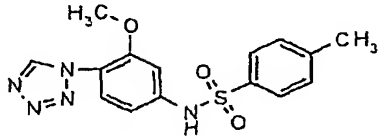
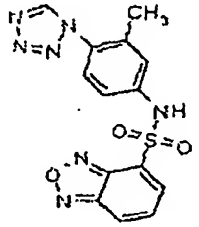
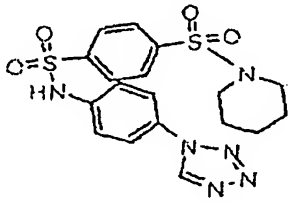
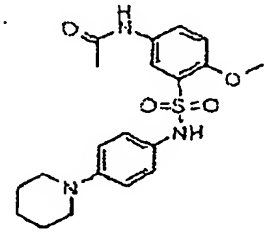
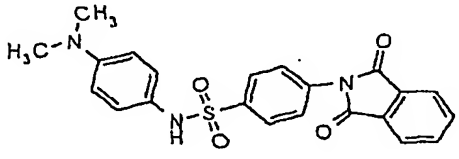
	316
	317
	318
	319
	320

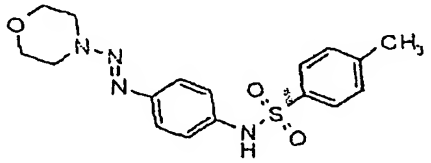
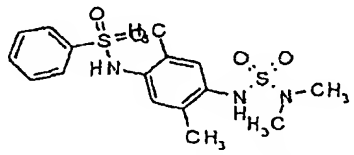
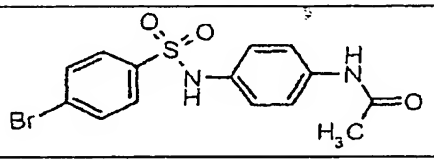
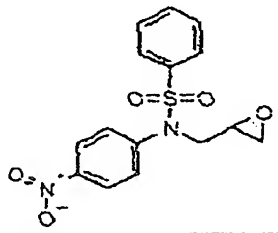
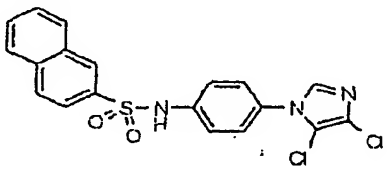
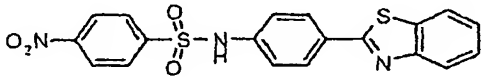
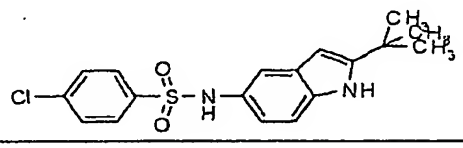
	321
	323
	324
	325
	326
	327
	328
	300

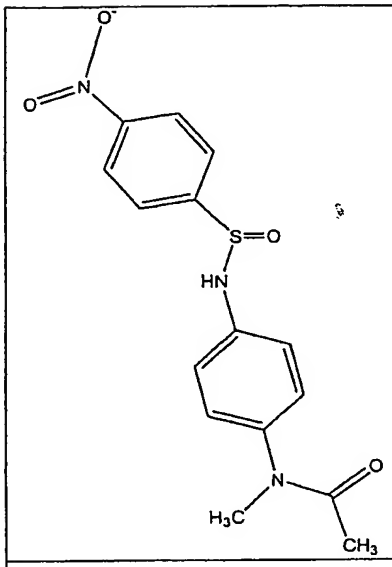
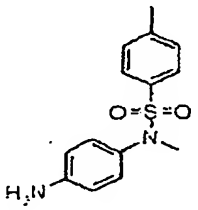
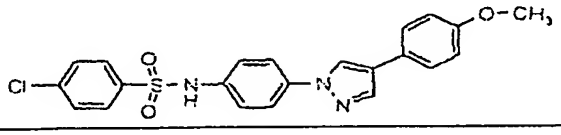
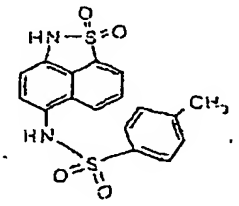
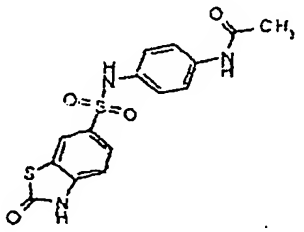
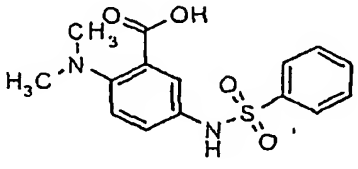
	130
	141
	167
	135
	136
	142
	137

	164
	165
	168
	163
	166
	131
	132
	133
	134

	138
	139
	140
	156
	157
	158
	159
	160
	161
	162
	143

	
	144
	145
	146
	147
	148
	149

	150
	
	151
	152
	
	
	

	
	
	
	
	
	153

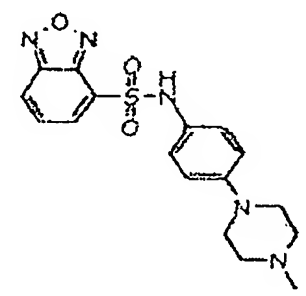
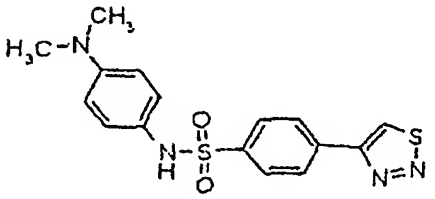
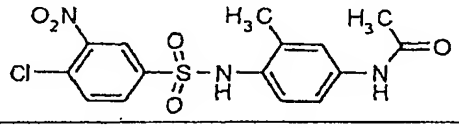
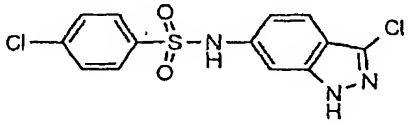
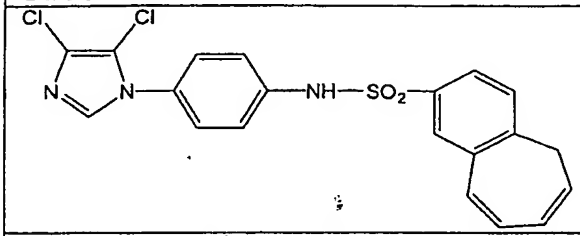
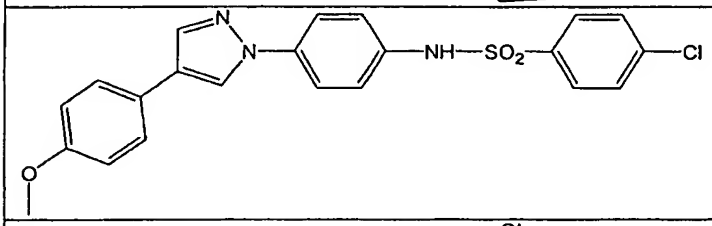
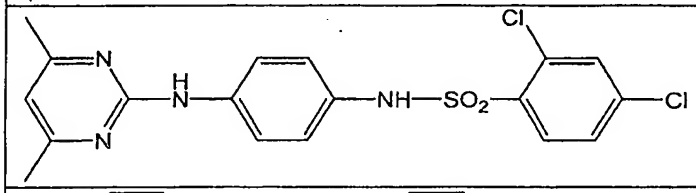
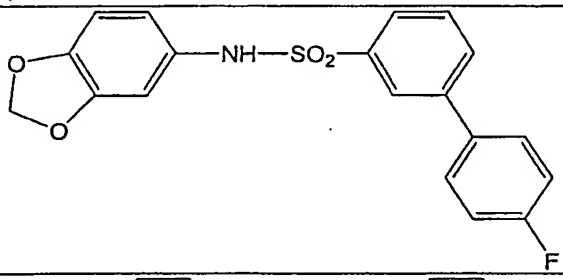
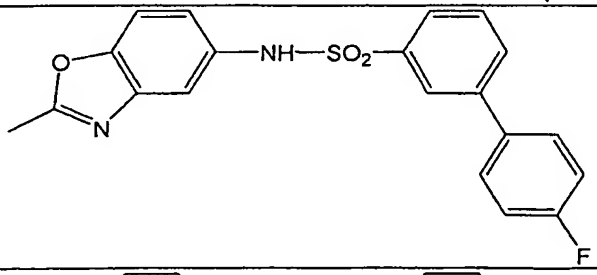
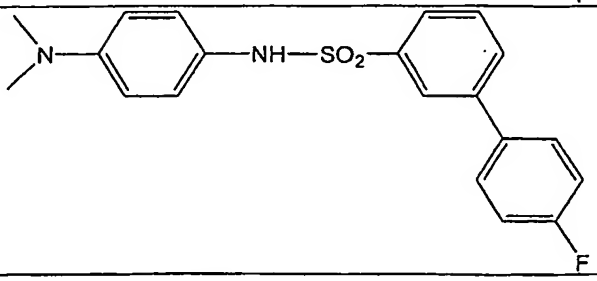
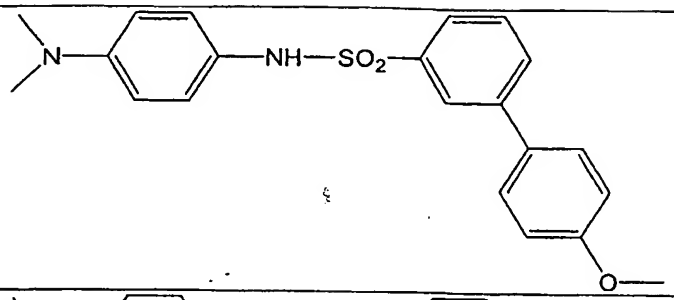
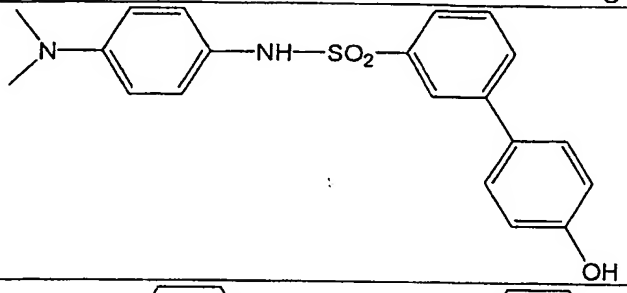
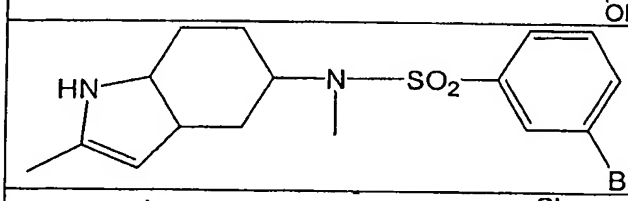
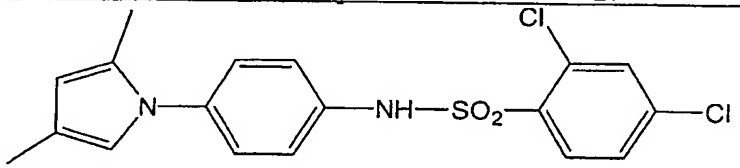
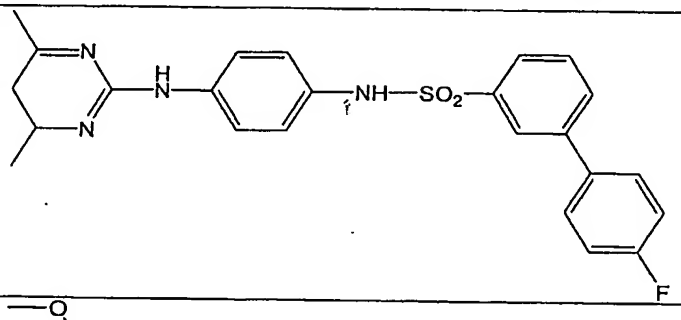
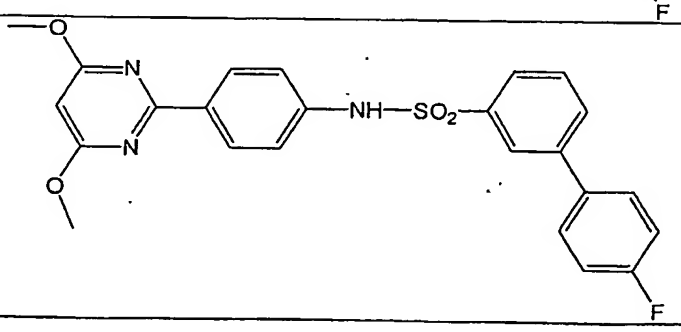
	154
	155
	
	

Table 1B

Structure	NCE number
	171
	176
	182
	186
	190
	203

	204
	205
	209
	213
	201
	235

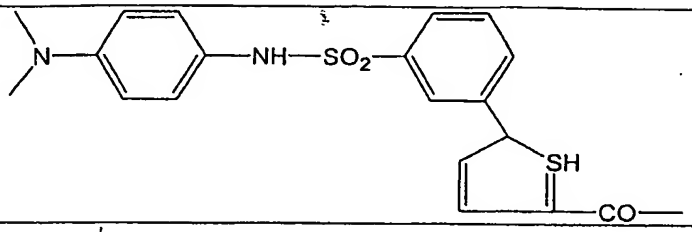
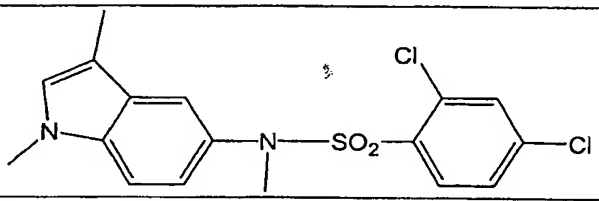
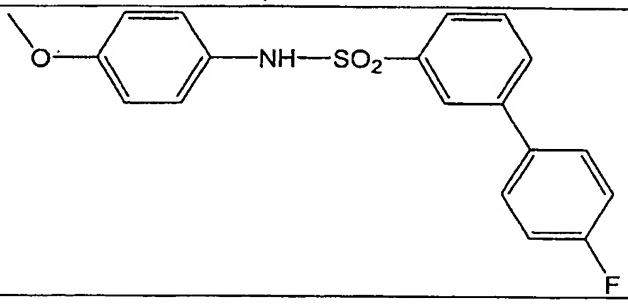
	239
	242
	250

Table 2

Compound	EC50 in cell adhesion assay	Emax in cell adhesion assay
NCE131	25 μM	58 %
NCE132	40 μM	90 %
NCE134	10 μM	40 %
NCE139	46 μM	75 %
NCE142	20 μM	77 %
NCE161	34 μM	82 %
NCE163	32 μM	66 % at 50 μM
NCE164	21 μM	85 % at 50 μM
NCE170	24 μM	85 % at 40 μM
NCE171	20 μM	79 %
NCE173	35 μM	59 % at 40 μM
NCE176	17 μM	59 % at 50 μM
NCE182	25 μM	77 %
NCE183	28 μM	81 %
NCE186	19 μM	91 %
NCE187	18 μM	87 %
NCE188	36 μM	81 %
NCE189	30 μM	76 %
NCE190	25 μM	76 %
NCE192	39 μM	75 %
NCE193	22 μM	72 %
NCE195	49 μM	60 %
NCE197	30 μM	74 %
NCE202	27 μM	91 %
NCE203	19 μM	86 %
NCE204	~25 μM (could not be defined by Prism)	63 %
NCE205	20 μM	84 % (50 μM)
NCE209	35 μM	64 % (50 μM)
NCE210	dd could not be detected	80 % (50 μM)
NCE213	25 μM	71 % (50 μM)

NCE201	36 μM	64 % (50 μM)
NCE222	15 μM	66 %
NCE223	13 μM	82 %
NCE230	>30 μM (could not be defined by Prism)	76 % (at 50 μM)
NCE234	35 μM	85 %
NCE235	20 μM	85 %
NCE239	24 μM	64 % (at 50 μM)
NCE242	6 μM	70 %
NCE250	31 μM	89 %
NCE255	17 μM	88 % (at 50 μM)
NCE258	40 μM	66 %
NCE263	26 μM	88 %
NCE266	18 μM	70 %
NCE269	19 μM	64 %
NCE275	26 μM	57 %
NCE281	47 μM	78 %
NCE282	1.6 μM	59% (at 50 μM)
NCE283	23 μM	63 %
NCE284	~30 μM	69 %
NCE285	20 μM	60 % (at 50 μM)
NCE286	37 μM	72 %
NCE291	32 μM	50 %
NCE295	29 μM	56 %
NCE297	26 μM	80 %
NCE298	33 μM	79 %
NCE299	9.6 μM	79 %
NCE302	24 μM	57 %
NCE306	24 μM	67 % (at 50 μM)
NCE307	20 μM	67 % (at 50 μM)
NCE300	45 μM	50 %
NCE316	10 μM	87 % (at 50 μM)
NCE317	44 μM	45 %
NCE320	10 μM	45 %
NCE321	6.3 μM	55 %

The test results showed that the compounds of the present invention have an anti-cancer and antithrombotic activity *in vitro*.

The following examples illustrate the invention but are not intended to limitate the scope of the invention.

Example 1

3-bromo-N-[4-(dimethylamino)phenyl]benzenesulphonamide

To a solution of 4-dimethylamino aniline (2 g, 0.0147 mol) and triethylamine (2.25 mL, 0.0162 mol, 1.1 eq.) in acetonitrile (20 mL) at 0°C under nitrogen was added dropwise a solution of 3-bromobenzene sulphonyl chloride (3.94 g, 0.0154 mol, 1.05 eq.) in acetonitrile (5 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was removed *in vacuo* and the residue redissolved in ethyl acetate (100 mL). The organic layer was washed with sat aqueous $NaHC-O_3$ (2x200 mL), water (2x200 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated. The product was obtained as a brown solid (3.5g, 67.0%) and was not purified further.

^1H NMR (300 MHz d_6 DMSO) δ 7.78 — 7.76 (s, 2ff), 7.61 — 7.58 (d, 1H), 7.48 — 7.43 (t, 1H), 6.84 — 6.80 (d, 2H), 6.57 — 6.54 (d, 2H), 2.78 (s, 6H); ^{13}C NIMR (300 MHz d_6 DMSO) δ 148.84, 142.15, 135.70, 131.65, 129.46, 126.12, 125.66, 124.77, 122.24, 112.95; LCMS R_t 15.44 min.; *m/z* — 353.3. MP 187-189°C.

Example 2

3',4'-dimethoxy-biphenyl-3-sulphonic acid (4-dimethylamino-phenyl)-amide (BTT-3002)

To a solution of 3-bromo-N-(4-dimethylamino-phenyl)-benzenesulphonamide (2.14 g, 6.02 mmol) and 3,4-dimethoxyphenyl-boronic acid (1.09 g, 6.02 mmol) in toluene (200 mL) and aqueous sodium carbonate solution (2 M, 100 mL) under N_2 was added tetrakis (triphenylphosphine) palladium (0) (80 mg). The mixture was stirred under reflux for 18 hours. The reaction mixture was then filtered through celite and washed with ethyl acetate. The organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent the crude material was purified by column chromatography (SiO_2, ethylacetate/cyclohexane = 4/6) to yield 1.8 g (73%) of NCE-102 as light yellow crystals: mp 43°C. ^1H NMR (300 MHz, $CDCl_3$) 8.2.93 (6 H, s), 3.94 (6 H, s), 6.19 (1

H, bs), 6.60 (2 H, d, J = 9 Hz), 6.9 (4 H, m), 7.09 (1 H, d, J = 9 Hz), 7.46 (1 H, t, J = 8.8 Hz), 7.64 (1 H, d, J 9 Hz), 7.5 (1 H, d, J 8.8 Hz, CH), 7.87 (1 H, s); ^{13}C NMR (300 MHz, $CDCl_3$) 840.88, 56.42, 56.45, 110.77, 112.01, 113.04, 120.05, 124.97, 125.76, 125.87, 126.80, 129.59, 131.18, 132.61, 140.21, 142.15, 149.76, 149.81; MS (ES^+) *m/z* 413.5 (M + H).

Example 3

N-[4-(dimethylamino)phenyl]-4'-fluoro-1,1'-biphenyl-3-sulphonamide (BTT-3003)

Crude compound of example 1 (3.98 g, 11.2 mmol), 4-fluorobenzene boronic acid (1.57 g, 11.2 mmol) and tetrakis (triphenylphosphine) palladium (160 mg, 0.14 mmol) were stirred in toluene (150 mL, degassed) and 2M sodium bicarbonate solution (100 mL, degassed) at 106°C overnight. After this time the reaction mixture was filtered through celite, the organic solution separated from the aqueous, which was washed with ethyl acetate and the organic solvents combined. The crude dark brown/black material was decolourised with activated charcoal and recrystallised from isopropanol to give the product (1.8324 g, 44%) as an off white/beige material: mp 158-160°C; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 6H), 6.69 (s, 1H), 6.72 (s, 2H), 7.05 — 7.08 (d, J= 9 Hz, 2H), 7.19 — 7.24 (t, J= 8.7 Hz, 2H), 7.52 — 7.62 (m, 3H), 7.79 — 7.8 1 (m, 2H), 7.94-7.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 40.93, 113.14, 116.085, 116.372, 125.02, 126.23, 126.71, 129.28, 129.73, 131.35, 135.81, 140,25, 141.30, 149.86, 161.64, 164.93, LCMS Rf= 15.0 mins, (ES) = *m/z* 371.3 (M + 1).

Example 4

2,4-dichloro-N-{4-[(4,6-dimethylpyrimidin-2-yl)(methyl)amino]phenyl}benzenesulphonamide (BTT-3001)

To a solution of N-(4,6-dimethylpyrimidin-2-yl)-N-methylbenzene-1,4-diamine (2 g, 0.0088 mol) and triethylamine (1.35 mL, 0.0097 mol, 1.1 eq.) in acetonitrile (30 mL) at 0°C under nitrogen was added dropwise a solution of 2,4-dichlorobenzene suiphonyl chloride (2.26 g, 0.0092 mol, 1.05 eq.) in acetonitrile (10 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was removed *in vacuo* and the residue redissolved in ethyl acetate (100 mL). The organic layer was washed with sat aqueous $NaHCO_3$ (2x100 mL), water (2x100 mL), brine (100 mL), dried (Na_2SO_4),

filtered and concentrated. The residue was purified by column chromatography (1:4 AcOEt:cyclohexane) to yield 1.26 g of a yellow oil (bis suiphonamide) and 1.77 g (46.2%) of a light green solid (monosulphonamide).

Bis sulphonamide: ^{1}H NMR (300 MHz $CDCl_3$) *8* 8.13 — 8.10 (d, 2H), 7.52 — 7.51 (d, 2H), 7.43 — 7.38 (dd, 1H), 7.37 — 7.34 (d, 2H), 7.26 — 7.22 (d, 2H), 6.43 (s, 1H), *3.56* (s, 3H), 2.29 (s, 6H).

Monosulphonamide: ^{1}H NMR (300 MHz $CDCl_3$) 8 7.88 — 7.85 (d, 1H), 7.46 (d, 111), 7.26 — 7.22 (dd, 1H), 7.18 — 7.14 (d, 2H), 7.01 — 6.98 (d, 2H), 6.87 (s, NH), 6.29 (s, 1H), 3.40 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (300 MHz $CDCl_3$) *δ* 167.35, 144.51, 140.29, 135.53, 133.39, 131.78, 131.59, 127.97, 126.99, 123.02, 110.88, 38.46, 24.39; LCMS R_t 18.71 min.; *m/z* — 437.4.

Example 5

Hydrolysis of the 2,4-dichloro-N-[(2,4-dichlorophenyl)sulphonyl]-N-{4-[(4,6-dimethylpyrimidin-2-yl)(methyl)amino]phenyl}benzenesulphonamide

To a solution of the bis sulphonamide (1.26 g, 0.002 mol) in ethanol (50 mL) was added NaOEt (653 mg, 0.0097 mol, 5 eq.) and the reaction was heated to 65°C for 5 hrs. The solvent was removed *in vacuo* and residue dissolved in water. The aqueous layer was washed twice with $CHCl_3$ (50 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated. The solid was purified by column chromatography (1:4 — 2:3 AcOEt:cyclohexane) to yield a beige solid (550 mg, 64.7%, 2,4-dichloro-N-{4-[(4,6-dimethylpyrimidin-2-yl)(methyl)amino]phenyl}benzenesulphonamide).

^{1}H NMR (300 MHz $CDCl_3$) *δ* 7.88 —7.87 (d, 1H), 7.46 (d, 1H), 7.26 — 7.22 (dd, 1H), 7.18 — 7.14 (d, 2H), 7.02 — 6.97 (d, 2H), 6.90 (s, NH), 6.28 (s, 1H), 3.40 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (300 MHz $CDCl_3$) 6 167.36, 144.49, 140.28, 135.54, 133.39, 131.72, 131.61, 127.97, 127.00, 123.00, 110.88, 38.47, 24.39; LCMS R_t 18.71 min.; *m/z* — 437.4.

LCMS conditions: 0-97% acetonitrile in water, C18, electrospray +ve.

Example 6

N-[4-(dimethylamino)phenyl]-3-(5-methyl-1,3,4-oxadiazol-2-yl)benzene-sulphonamide

To a solution of 4-dimethyl amino aniline (0.05 g, 0.367 mmol) and triethylamine (0.056 mL, 0.404 mmol, 1.1 eq.) in acetonitrile (2 mL) under nitrogen was added 3-(5-methyl-1,3,4-oxadiazol-2-yl) benzene sulphonyl chloride (0.0997 g, 0.385 mmol, 1.05 eq.) in acetonitrile (2 mL). The mixture was shaken at room temperature for 18 hours. The solvent was removed *in vacuo*. The residue was re-dissolved in AcOEt and the organic layer washed with saturated aqueous $NaHCO_3$, separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was analysed by LCMS and was shown to be mainly product (R_t 9.97 min; *m/z* — 359.3). The residue was purified by MS-directed prep HPLC to give the sulphonamide as a black solid (5.6 mg).

^1H NMR (300 MHz $CDCl_3/d_4$ MeOH (2 drops)) δ 8.29 — 8.27 (m, 1H), 8.04 — 8.01 (m, 1H), 7.97 — 7.94 (m, 1H), 7.81 — 7.75 (m, 1H), 7.52 — 7.46 (t, 1H), 7.02 — 6.97 (m, 4H), 2.96 (s, 6H), 2.67 (s, 3H); Purity - >95%.

Example 7

2,4-dichloro-N-[4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-phenyl]benzenesulphonamide

To bromo wang resin in DMF (4 ml) was added 1-(4-aminophenyl)-2, 6, 6-trimethyl-5,6,7-trihydroindol-4-one (0.375 g, 1.40 mmol, 5 eq.), sodium iodide (0.210 g, 1.40 mmol, 5 eq.) and disopropylethylamine (0.500 ml, 2.80 mmol, 10 eq.). The resin was shaken at 90°C for 24hrs. The resin was filtered and washed with 5ml of DMF, DCM, DMF, DCM, MeOH, DCM, MeOH and finally Et_2O. The resin was dried under vacuum.

To the resin was added pyridine (3 ml), 2,4-dichlorobenzene sulphonyl chloride (0.430 g, 1.75 mmol, 5 eq.) and DMAP (0.085 g, 0.700 mmol, 2 eq.). The resin was shaken at 60°C for 18hrs and washed with 5ml of DMF, DCM, DMF, DCM, MeOH, DCM, MeOH and finally Et_2O.

The resin was shaken in a solution of 95% TFA / 5% H_2O (3 ml) for 24hrs, filtered and the resin washed with DCM (1 ml) and MeOH (1 ml). The combined filtrates were concentrated *in vacuo*. The residue was purified by MS-directed prep HPLC to give the sulphonamide (1.1 mg).

LCMS R_t 11.46 min.; *m/z* — 478; Purity -85%.

Example 8

2,4-dichloro-N-(2-methyl-1,3-benzothiazol-5-yl)benzenesulphonamide

To a solution of 2-methyl-1, 3-benzothiazol-5-amine (0.05 g, 0.211 mmol, 1 eq.) in acetonitrile (2 ml) was added triethyl amine (0.059 ml, 0.232 mmol, 1.1 eq.) and 2,4 dichlorobenzene sulphonyl chloride (0.054 g, 0.222 mmol, 1.05 eq.). The mixture was shaken at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue dissolved in AcOEt. The AcOEt was washed with saturated aqueous $NaHCO_3$, separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by MS-directed prep HPLC to yield the sulphonamide (3.1 mg).

LCMS R_t 11.15 min.; *m/z* — 374; Purity -95%.

Example 9

4-bromo-N-[4-(dimethylamino)phenyl]benzenesulphonamide

To a solution of 4-dimethyl amino aniline (2 g, 0.0147 mol) and triethylamine (2.25 mL, 0.0162 mol, 1.1 eq.) in acetonitrile (20 mL) at 0°C under nitrogen was added 4-bromo-benzene sulphonyl chloride (3.94 g, 0.0154 mol, 1.05 eq.). The mixture was cooled to 0°C for 30 mins, and then allowed to warm to room temperature. The reaction was stirred for 18 hours. The solvent was removed *in vacuo* and the residue redissolved in ethyl acetate (100 mL). The organic layer was washed with sat aqueous $NaHCO_3$ (2x200 mL), water (2x200 mL), brine (200 mL), separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in DCM, filtered through a pad of silica and the pad washed twice with DCM (100 ml). The filtrates were combined and concentrated *in vacuo*. The sulphonamide was obtained as a orange coloured solid (4.01g, 76.6 %).

^{1}H NMR (300 MHz $CDCl_3$) δ 7.47 (s, 4H), 6.83 — 6.71 (d, 2H), 6.50 — 6.46 (d, 2H), 6.31 (b s, 1H), 2.83 (s, 6H); ^{13}C NMR (300 MHz $CDCl_3$) δ 149.92, 138.83, 132.47, 129.32, 128.00, 126.77, 124.40, 113.07, 40.86; LCMS R_t 11.57 min.; *m/z* — 356:358 (1:1 ratio).

Example 10

N-[4-(dimethylamino)phenyl]-4-(1-naphthyl)benzenesulfonamide

4-bromo-N-[4-(dimethylamino)phenyl]benzenesulphonamide (25 mg, 0.07 mmol) and 1-naphthyl boronic acid (17.2 mg, 0.07 mmol, 1 eq.) was dissolved in toluene (2 ml) under N_2. Saturated aqueous Na_2CO_3 (1 ml) was added followed by palladium tetrakis(triphenylphosphine) (1 mg, cat.). The reaction was refluxed for 4 hrs and then left to stirring at room temperature for 18 hrs. The reaction was diluted with AcOEt (4 ml) and the organic layer decanted off. The organic layer was filtered through a pad of celite and the solvent removed *in vacuo*. The residue was analysed by LCMS and confirmed to be the sulphonamide product (17.2 mg, 60.4%).

LCMS R_t 12.91 min.; *m/z* — 404; Purity -95%.

The compounds of example 11 to 37 were prepared according to the following general coupling procedure.

General Coupling Procedure 1: Coupling of sulfonyl chloride to amine in acetonitrile

To a stirred solution of the amine (0.75 mmol) and triethylamine (0.75 mmol) in anhydrous acetonitrile (1 ml) at 0 °C was added 2, 4-dichlorobenzenesulphonyl chloride (0.50 mmol) in acetonitrile (1 ml). The mixture was stirred at this temperature for 2-3 hours and/or warmed up to ambient temperature and stirred until reaction had completed by TLC.

The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (25 ml) and saturated aqueous sodium bicarbonate solution (25 ml). The organic layer was separated and further washed with sodium bicarbonate (2x25ml), brine (2x25ml), dried over sodium sulphate and concentrated down. The product was purified either by flash chromatography or preparative HPLC.

Example 11

NCE131 2,4-Dichloro-N-(2-methyl-1H-indol-5-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.38 (3H, s, 2'-C$\underline{H}_3$), 6.11 (1H, m, 3'-H), 6.84 (1H, dd, J 2.1 and 8.5 Hz), 6.96 (1H, s), 7.09 (1H, d, J 8.5 Hz), 7.16 (1H,

dd, J 2.0 and 8.5 Hz), 7.23 (1H, d, J 2.0 Hz), 7.50 (1H, d, J 2.0 Hz), 7.77 (1H, d, J 8.5 Hz), 7.93 (1H, br, N-H)

^{13}C NMR (300 MHz, $CDCl_3$) 13.69 (CH_3), 100.66 (3'-CH), 110.75 (CH), 115.44 (CH), 117.83 (CH), 127.14, 127.45 (CH), 129.35, 131.17 (CH), 132.24, 132.99 (CH), 134.74, 135.07, 136.80, 139.51

Actual Mass: 354.95

LCMS: Mass detected $[M-H]^-$ 353.00; Retention time 17.2 mins; Purity 87%

Example 12

NCE132 2,4-Dichloro-N-(2-methyl-benzothiazol-5-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.79 (3H, s, 2'-CH_3), 7.18-7.28 (3H, m, 3xAr-H), 7.49 (1H, d, J 2.0 Hz), 7.67 (1H, d, J 8.6 Hz), 7,94 (1H, d, J 11.5 Hz)

^{13}C NMR (300 MHz, $CDCl_3$) 20.19 (CH_3), 115.59 (CH), 119.82 (CH), 122.13 (CH), 127.65 (CH), 131.46 (CH), 132.26, 133.04 (CH), 133.44, 134.61, 140.08, 153.89, 169.12

Actual Mass: 404.85

LCMS: Mass detected $[M-H]^-$ 402.85; Retention time 16.6 mins; Purity 96%

Example 13

NCE133 2,4-Dichloro-N-(2-methyl-benzothiazol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.78 (3H, s, 2'-CH_3), 7.12 (1H, dd, J 2.2 and 8.7 Hz), 7.15 (1H, br, N-H), 7.27 (1H, dd, J 2.0 and 8.5 Hz), 7.52 (1H, d, J 2.0 Hz), 7.67 (1H, d, J 2.2 Hz), 7.76 (1H, d, J 8.7 Hz), 7.88 (1H, d, J 8.5 Hz)

Actual Mass: 373.00

LCMS: Mass detected $[M-H]^-$ 370.95; Retention time 13.2 mins; Purity 97%

Example 14

NCE134 2,4-Dichloro-N-(1H-indol-5-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.04 (3H, s, 2'-C<u>H</u>$_3$), 6.45-6.46 (1H, m), 6.94 (1H, dd, J 2.0 and 8.6 Hz), 7.00 (1H, s), 7.17-7.25 (3H, m), 7.38 (1H, d, J 1.6 Hz), 7.52 (1H, d, J 2.0 Hz), 7.80 (1H, d, J 8.5 Hz), 8.25 (1H, br, N-<u>H</u>)

Actual Mass: 341.00

LCMS: Mass detected $[M-H]^-$ 339.05; Retention time 13.2 mins; Purity 96%

Example 15

NCE138 2,4-Dichloro-N-(benzothiazol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 7.22 (1H, dd, J 2.2 and 8.7 Hz), 7.28 (1H, dd, J 2.0 and 8.5 Hz), 7.51 (1H, d, J 2.0 Hz), 7.56 (1H, br, N-<u>H</u>), 7.82 (1H, d, J 2.1 Hz), 7.94 (2H, dd, J 8.7 and 13.3 Hz), 8.94 (1H, s, 2'-<u>H</u>)

Actual Mass: 358.90

LCMS: Mass detected $[M-H]^-$ 356.90; Retention time 12.2 mins; Purity 88%

Example 16

NCE139 N-Benzolthiazol-6-yl-3-bromo-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

NMR-To be purified and determined.

Actual Mass: 369

LCMS: No ionization; Retention time 10.3 mins; Purity 93%

Example 17

NCE140 3-Bromo-N-(2-methyl-benzothiazol-5-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.80 (3H, s, 2'-C<u>H</u>$_3$), 7.18 (1H, dd, J 2.1 and 8.6Hz), 7.26 (1H, dd, J 2.7 and 10.6Hz), 7.33 (1H, br, N-<u>H</u>), 7.60-7.72 (4H, m, 4xAr-<u>H</u>), 7.94 (1H, m, Ar-<u>H</u>)

Actual Mass: 383

LCMS: No ionization; Retention time 17.1 mins; Purity 93%

Example 18

NCE156 2,4-Dichloro-N-(2-methyl-benzooxazol-5-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.59 (3H, s, 2'-C<u>H</u>$_3$), 7.07 (1H, br, N-H), 7.11 (1H, dd, J 2.2 and 8.6 Hz), 7.24 (1H, dd, J 2.0 and 8.6 Hz), 7.34 (1H, d, J 8.6 Hz), 7.38 (1H, d, J 2.0 Hz), 7.52 (1H, d, J 2.0 Hz), 7.84 (1H, d, J 8.6 Hz)

Actual Mass: 356.80

LCMS: Mass detected $[M-H]^-$ 355.00; Retention time 17.6 mins; Purity 80%

Example 19

NCE157 N-Benzo[1,3]dioxol-5-yl-2,4-dichloro-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 5.92 (2H, s, 2'-C<u>H</u>$_2$), 6.50 (1H, dd, J 2.1 and 8.3 Hz), 6.61 (1H, d, J 8.3 Hz), 6.70 (1H, d, J 2.1 Hz), 6.93 (1H, br, N-<u>H</u>), 7.30 (1H, dd, J 2.2 and 8.5 Hz), 7.53 (1H, d, J 2.0 Hz), 7.86 (1H, d, 8.5 Hz)

Actual Mass: 345.95

LCMS: Mass detected $[M-H]^-$ 343.80; Retention time 14.3 mins; Purity 97%

Example 20

NCE158 3-Bromo-N-(2-methyl-benzooxazol-5yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.62 (3H, s, 2'-C<u>H</u>$_3$), 6.70 (1H, br, N-<u>H</u>), 7.06 (1H, dd, J 2.2 and 8.6 Hz), 7.25-7.31 (2H, m 2xAr-<u>H</u>), 7.37 (1H, d, J 8.6 Hz), 7.59-7.64 (2H, m, 2xAr-<u>H</u>), 7.90 (1H, t, J 1.8 Hz)

Actual Mass: 367.00

LCMS: Mass detected $[M-H]^-$ 365.00; Retention time 11.1 mins; Purity 86%

Example 21

NCE159 N-Benzo[1,3]dioxol-5-yl-3-bromo-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 5.95 (2H, s, 2'-C<u>H</u>$_2$), 6.44 (1H, dd, J 2.2 and 8.3 Hz), 6.65 (1H, d, J 8.3 Hz), 6.67 (1H, d, J 2.2 Hz), 6.80 (1H, br, N-<u>H</u>), 7.32 (1H, t, J 7.9 Hz), 7.65 (2H, dt, J 0.9 and 7.9 Hz), 7.90 (1H, t, J 1.8 Hz)

Actual Mass: 356.00

LCMS: Mass detected $[M-H]^-$ 353.95; Retention time 13.4 mins; Purity 98%

Example 22

NCE-160 2,4-Dichloro-N-(2-methyl-benzooxazol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.59 (3H, s, 2'-C<u>H</u>$_3$), 7.00 (1H, dd, J 3.1 and 6.4 Hz), 7.26 (1H, dd, J 2.0 and 8.5 Hz), 7.39 (1H, d, J 2.0 Hz), 7.43 (1H, d, J 4.7 Hz), 7.49 (1H, d, J 2.0 Hz), 7.67 (1H, br, N-<u>H</u>), 8.17 (1H, d, J 8.5 Hz)

Actual Mass: 357.00

LCMS: Mass detected $[M-H]^-$ 355.00; Retention time 11.7 mins; Purity 99%

Example 23

NCE 169 3-Bromo-N-(2-methyl-benzooxazol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 2.62 (3H, s, 2'-C<u>H</u>$_3$), 6.91 (1H, dd, J 2.0 and 8.4 Hz), 7.28 (1H, t, J 7.9 Hz), 7.38-7.40 (2H, m), 7.47 (1H, d, J 8.5 Hz), 7.61-7.66 (2H, m), 7.9 (1H, t, J 1.8 Hz)

Actual Mass: 366.95

LCMS: Mass detected $[M-H]^-$ 364.90; Retention time 10.6 mins; Purity 89%

Example 24

NCE161 2,4-Dichloro-N-(1H-indol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 6.47 (1H, m), 6.76 (1H, dd, J 1.9 and 8.4 Hz), 7.50 (1H, s), 7.18-7.26 (3H, m), 7.32 (1H, s), 7.44 (1H, d, J 8.4 Hz), 7.51 (1H, d, J 2.0 Hz), 7.82 (1H, d, J 8.5 Hz), 8.21 (1H, br, N-<u>H</u>)

Actual Mass: 341.05

LCMS: Mass detected $[M-H]^-$ 339.05; Retention time 14.1 mins; Purity 99%

Example 25

NCE162 3-Bromo-N-(1H-indol-6-yl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR (300 MHz; $CDCl_3$) 6.51 (1H, m), 6.57 (1H, s), 6.64 (1H, dd, J 1.9 and 8.4 Hz), 7.22 (1H, dd, J 2.4 and 5.6 Hz), 7.33 (1H, s), 7.47 (1H, d, J 8.4 Hz), 7.55-7.62 (2H, m), 7.91 (1H, t, 1.8 Hz), 8.22 (1H, br, N-<u>H</u>)

Actual Mass: 350.90

LCMS: Mass detected $[M-H]^-$ 348.90; Retention time 12.9 mins; Purity 98%

Example 26

NCE 130 4-Bromo-2-chloro-N-(4-dimethylamino-phenyl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 300 MHz; δ_H ($CDCl_3$) 7.73 (1H, d, *J 8.4Hz*, ArH), 7.69 (1H, d, *J 2.0Hz*, ArH), 7.41 (1H, dd, *J 2.0, 8.4Hz*, ArH), 6.97 (2H, d, *J 8.8Hz*, ArH), 6.54 (2H, d, *J 8.8Hz*, ArH), 2.90 (6H, s, $N(CH_3)_2$).

ESMS +ve calculated 389.7, $[M+H]^+$ 389.17. Purity Estimated >90%

Example 27

NCE 141 4-Bromo-N-(2,4-dichloro-phenyl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 400 MHz δ_H (DMSO) 7.93 (4H, m, ArH), 7.75 (2H, dd, *J 2.0, 7.2 Hz), 7.32 (1H, J 7.2Hz*, ArH).

Actual Mass: 381.08

LCMS: Mass detected $[M-H]^-$ no ionisation; Retention time 16.25 mins; Purity 95.2%

Example 28

NCE 167 4-Bromo-N-(3,4-dichloro-phenyl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 400 MHz δ_H (DMSO) 7.92 (2H, d, *J 8.8Hz*, ArH), 7.67 (2H, d, *J 8.8Hz*, ArH). 7.66 (1H, d, ArH), 7.50 (1H, d, *J 2.0Hz*, ArH), 7.04 (1H, dd, *J 2.0, 7.6Hz*, ArH).

Actual Mass: 381.08

LCMS: Mass detected $[M-H]^-$ 380.10; Retention time 21.57 mins; Purity 92.1%

Example 29

NCE 135 [4-(2,4-Dichloro-benzenesulfonylamino)-phenyl]-(4,6-dimethyl-pyrimidin-2-yl)-methyl-ammonium; chloride

NCE 50 2,4-dichloro-N-{4-[(4,6-dimethyl-pyrimidin-2-yl)-methyl-amino]-phenyl}-benzenesulfonamide (75mg, 1.7mM) was dissolved in ethyl acetate (10ml) with stirring. To this solution was carefully added a solution of 2M hydrochloric acid in diethyl ether (1ml). A white precipitate is then observed. This solid was filtered off, washed with diethyl ether and dried under high vacuum. The salt produced was redissolved in distilled water with a minimum of acetonitrile to ensure complete solubility and freeze dried to yield an off white solid.

^{1}H NMR 300 MHz δ_H (CD_3OD) 9.37 (1H, d, *J 8.4Hz*, ArH), 8.98 (1H, d, *J 2.0Hz*, ArH), 8.83 (1H, dd, *J 2.0, 8.4Hz*, ArH), 8.57 (4H, m, ArH), 7.94 (1H, s, Pyrimidyl), 3.50 (6H, $ArCH_3$).

Purity Estimated >90%

Example 30

NCE 136 Methanesulfonate[4-(2,4-dichloro-benzenesulfonylamino)-phenyl]-(4,6-dimethyl-pyrimidin-2-yl)-methyl-ammonium

NCE 50 2,4-dichloro-N-{4-[(4,6-dimethyl-pyrimidin-2-yl)-methyl-amino]-phenyl}-benzenesulfonamide (75mh, 1.7mM) was dissolved in ethyl acetate (10ml) with stirring. To this solution is added a solution of methane sulfonic acid in ethyl acetate (1M, 2ml), this solution was then evacuated to dryness to yield a light brown oil. The oil was repeatedly suspended in dry diethyl ether and the solvent decanted off to remove excess acid. The salt produced was the redissolved in distilled water with a minimum of acetonitrile to ensure complete solubility and freeze dried to yield a brown oil.

^{1}H NMR 300 MHz δH (CD_3OD) 9.46 (1H, d, *J 8.4Hz*, ArH), 9.01 (1H, d, *J 2.0Hz*, ArH), 8.88 (1H, dd, *J 2.0, 8.4Hz*, ArH), 8.74 (2H, d, ArH), 8.66 (2H, d, ArH), 8.24 (1H, s, Pyrimidyl), 4.83 (3H, s), 3.75 (6H, $ArCH_3$).

Purity Estimated >90%

Example 31

NCE 142 [4-(3',4'-Dimethoxy-biphenyl-3-sulfonylamino)-phenyl]-dimethyl-ammonium; chloride

Procedure used identical to that for NCE 135 using NCE 102 as the starting material.

^{1}H NMR 400 MHz δ_H ($CDCl_3$) 7.94 (1H, s, ArH), 7.89 (1H, d, *J 7.6Hz*, ArH), 7.65 (1H, d, *J 7.6Hz*, ArH), 7.58 (1H, t, *J 7.6Hz*, ArH), 7.05-7.16 (7H, m, ArH), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.92 (6H, s, $N(CH_3)_2$)

Purity Estimated >90%

Example 32

NCE 137 4-Bromo-2-chloro-N-{4-[(4,6-dimethyl-pyrimidin-2-yl)-methyl-amino]-phenyl}-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography

^{1}H NMR 400 MHz δ_H ($CDCl_3$) 7.78 (1H, d, *J 8.8 Hz*, ArH), 7.69 (1H, s), 7.48 (1H, d, *J 8.8Hz*, ArH), 7.25 (2H, d, *J 8.7Hz*, ArH), 7.06 (2H, d, *J 8.7Hz*, ArH), 6.37 (1H, s, Pyrimidyl), 3.48 (3H, s), 2.25 (6H, s).

Actual Mass: 481.80

LCMS: Mass detected $[M-H]^-$ 481.30; Retention time 16.58 mins; Purity 96.6%

Example 33

NCE 164 2,4-Dichloro-N-[4-(4,6-dimethoxy-pyrimidin-2-yl)-phenyl]-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 300 MHz δ_H ($CDCl_3$) 8.6 (2H, d, *J 7.6Hz*, ArH), 7.98 (1H, d, *J 8.5Hz*, ArH), 7.49 (1H, d, *J 2.0Hz*, ArH), 7.30 (1H, dd, *J 2.0, 8.5Hz*, ArH), 7.18 (2H, d, *J 7.5Hz*, ArH), 7.14 (1H, br s, NH), 5.93 (1H, s, Pyrimidyl), 4.00 (6H, s, OCH_3).

Actual Mass: 440.30

LCMS: Mass detected $[M-H]^-$ No Ionisation; Retention time 16.04 mins; Purity 96.9%

Example 34

NCE 165 2,4-Dichloro-N-[4-(4,6-dimethyl-pyrimidin-2-yloxy)-phenyl]-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 300 MHz δ_H ($CDCl_3$) 7.91 (1H, d, *J 8.5Hz*, ArH), 7.54 (1H, d, *J 2.0Hz*, ArH), 7.31 (1H, dd, *J 2.0, 8.5Hz*, ArH), 7.12 (4H, m, AB d), 6.96 (1H, br s, NH), 6.76 (1H, s, pyrimidyl), 2.37 (6H, s).

Actual Mass: 424.31

LCMS: Mass detected $[M-H]^-$ 422.40; Retention time 13.59 mins; Purity 97.0%

Example 35

NCE 168 2,4-Dichloro-N-[4-(4,6-dimethyl-pyrimidin-2-ylsulfonyl)-phenyl]-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by flash chromatography.

^{1}H NMR 400 MHz δH ($CDCl_3$) 7.95 (1H, d, *J 8.5Hz*, ArH), 7.49 (1H, d, *J 2.0Hz*, ArH), 7.45 (1H, d, *J 8.4Hz*, ArH), 7.30 (1H, dd, *J 2.0, 8.4Hz*, ArH), 7.11 (2H, d, *J 8.4Hz*, ArH), 6.67 (1H, br s, NH), 2.27 (6H, s, CH_3)

Actual Mass: 440.37

LCMS: Mass detected $[M-H]^-$ 438.40; Retention time 16.25 mins; Purity >95%

Example 36

NCE 163 2,4-Dichloro-N-(4-pyrrol-1-yl-phenyl)-benzenesulfonamide

Synthesised according to general coupling procedure 1 and purified by prep HPLC.

^{1}H NMR 300 MHz δ_H ($CDCl_3$) 7.90 (1H, d, *J 8.4Hz*, ArH), 7.54 (1H, d, *J 2.0Hz*, ArH), 7.30 (1H, dd, *J 2.0, 8.4Hz*, ArH), 7.25 (2H, d, ArH), 7.17 (2H, d, ArH), 6.98 (2H, t, *J 2.0Hz*, Pyrrole), 6.31 ((2H, t, *J 2.0Hz*, Pyrrole).

Actual Mass: 367.27

LCMS: Mass detected $[M-H]^-$ 365.20; Retention time 16.55 mins; Purity 96.8%

Example 37

NCE 166 Biphenyl-3-sulfonic acid (4-dimethylamino-phenyl)-amide

Synthesised according to general coupling procedure 1 and purified by Prep HPLC.

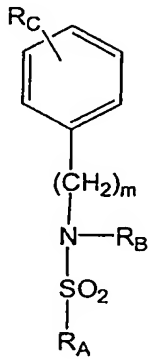
^{1}H NMR 400 MHz δ_H ($CDCl_3$) 7.82 (1H, t, ArH), 7.73 (1H, td, *J 7.8Hz*, ArH), 7.64 (1H, td, *J 7.8Hz*, ArH), 7.33-7.49 (6H, m, ArH), 6.90 (2H, d, *J 8.8Hz*, ArH), 6.56 (2H, d, ArH), 6.12 (1H, br s, ArH), 2.90 (6H, s, $N(CH_3)_2$.

Actual Mass: 352.46

LCMS: Mass detected $[M-H]^-$ 351.4.; Retention time mins; Purity 98.5 %

Claims

1. A sulphonamide derivative of formula (I),



(I)

where

R_C is an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or R_C is $-NR^1R^2$, where

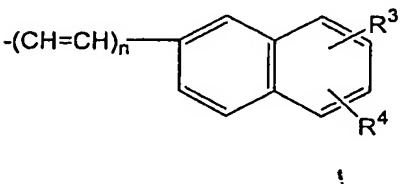
R^1 is hydrogen or alkyl,

R^2 is alkyl or an optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or

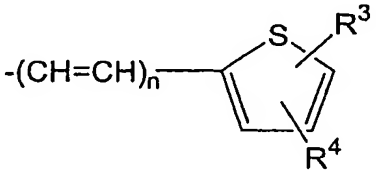
R^1 and R^2 taken together with the nitrogen atom to which they are attached form a heterocyclic group, which may contain one or more additional heteroatoms selected from O and N and which may be substituted, or

R^1 and R^2 are absent and the nitrogen atom together with the adjacent carbon atom forms a heterocyclic ring, which may contain one or more additional heteroatoms selected from N and S and which may be substituted,

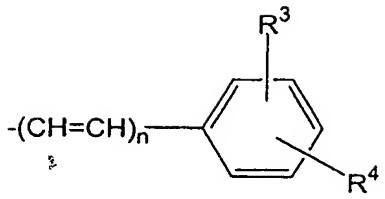
R_A is a group having the formula



(A),



(B) or



(C)

wherein

n is 0 or 1, and

R^3 and R^4 represent each independently hydrogen, halogen, aryl, alkoxy, carboxy, hydroxy, alkoxyalkyl, alkoxycarbonyl, cyano, trifluoromethyl, alkanoylamino, trifluorometoxy, an optionally substituted aryl or heterocyclic group.

2. A derivative according to claim 1 where R^1 and R^2 represent methyl, R^3 is 2-chloro and R^4 is 4-chloro.

3. A derivative according to claim 1 where R^1 is hydrogen, R^2 is 4,6-dimethylpyrimidin-2-yl, R^3 is chloro and R^4 is chloro.

4. A derivative according to claim 1 where R^1 and R^2 represent methyl, R^3 is hydrogen and R^4 is 3,4-dimethoxyphenyl.

5. A derivative according to claim 1 where R^1 and R^2 represent methyl, R^3 is hydrogen and R^4 is 4-fluorophenyl.

6. A derivative according to claim 1 where R^1 and R^2 represent methyl, R^3 is hydrogen and R^4 is bromo.

7. A derivative according to any of claims 1 to 6 for use as an inhibitor for collagen receptor integrins.

8. A derivative according to any of the claims 1 to 6 for use as an inhibitor for $\alpha 2\beta 1$ integrin.

9. A derivative according to any of claims 1 to 6 for use as an $\alpha 2\beta 1$ integrin I domain inhibitor.

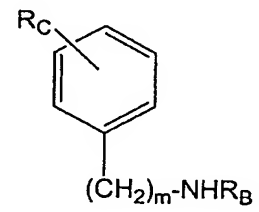
10. A derivative according to any of claims 1 to 6 for use as a medicament.

11. A derivative according to claim 10 for use as a medicament for treating thrombosis and cancer spread.

12. The use of a derivative according to any of claims 1 to 6 for preparing a pharmaceutical composition for treating disorders relating to thrombosis and cancer spread.

13. A pharmaceutical composition comprising an effective amount of a derivative according to any of claims 1 to 6 in admixture with a pharmaceutically acceptable carrier.

14. A process for preparing a benzene sulphonamide according to claim 1, comprising reacting a compound of formula (II)



(II)

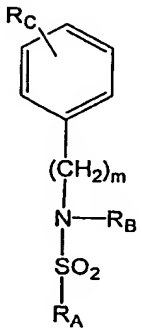
where R_B, R_C and m are as defined above, with a compound of formula (III)

$$R_A\text{-}SO_2hal \qquad (III)$$

where R_A is as defined above and hal is halogen.

(57) Abstract

The invention relates to sulphonamide derivatives of formula (I),



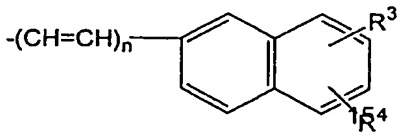
(I)

where

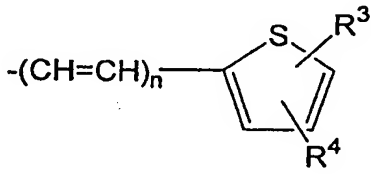
R_C is optionally substituted 4-6-membered heterocyclic ring containing one or more N atoms, or

R_C is $-NR^1R^2$,

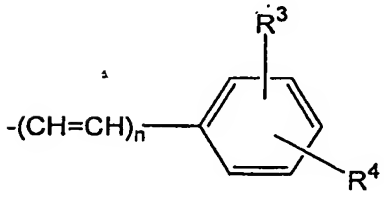
R_A is a group having the formula



(A),



(B) or



(C)

R_B is hydrogen or alkyl.

The invention also relates to the use of derivatives of formula (I) as inhibitors for collagen receptor integrins and a process for preparing sulphonamides of formula (I).

Fig 1 Invasion of PC-3 (prostate cancer) cell line through Matrigel

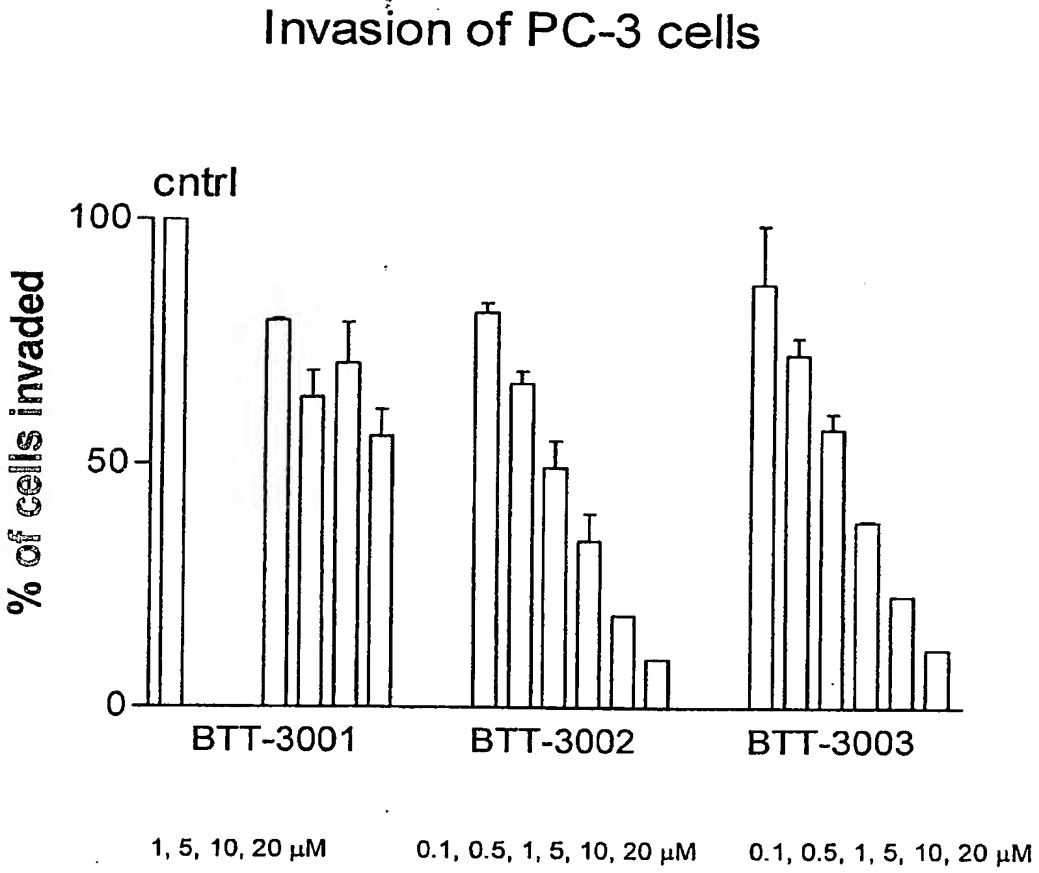


Fig 2 Representative result from PFA100 analysis